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The causal web of foetal alcohol spectrum disorders: a review and causal diagram

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Abstract

Foetal alcohol spectrum disorders (FASDs) are a leading cause of developmental disability. Prenatal alcohol use is the sole necessary cause of FASD, but it is not always sufficient. Multiple factors influence a child's susceptibility to FASD following prenatal alcohol exposure. Much of the FASD risk factor literature has been limited to discussions of association, rather than causation. While knowledge of predictor variables is important for identifying who is most at risk of FASD and for targeting interventions, causal knowledge is important for identifying effective mechanisms for prevention and intervention programmes. We conducted a systematic search and narrative synthesis of the evidence and used this to create a causal diagram (directed acyclic graph; DAG) to describe the causal pathways to FASD. Our results show that the aetiology of FASD is multifaceted and complex. FASD risk is determined by a range of lifestyle, sociodemographic, maternal, social, gestational, and genetic factors. The causal diagram that we present in this review provides a comprehensive summary of causal risk factors for FASD and can be used as a tool to inform data collection and statistical modelling strategies to minimise bias in future studies of FASD.

Keywords Foetal alcohol spectrum disorders · Causal diagram · Directed acyclic graph · Causal inference · Review · Prenatal exposures

Introduction

Foetal alcohol spectrum disorder (FASD) is an umbrella term that is used to describe a range of lifelong disabilities caused by prenatal alcohol exposure [1]. Individuals with FASD have neurodevelopmental impairments and some will also have growth deficiency and a distinctive facial phenotype, characterised by a thin upper lip, smooth philtrum and short palpebral fissure length [2]. Conservative estimates suggest that around 2–5% of children in the general

population of Europe and North America have FASD, making it one of the leading causes of preventable developmental disability worldwide [3, 4]. Maternal alcohol use is the sole necessary cause of FASD, but it is not always sufficient [5]. Among women who drink any amount of alcohol in pregnancy, an estimated one in 13 will have a child with FASD and one in 67 will have a child with foetal alcohol syndrome (FAS) [4, 6]. Alcohol interacts with multiple factors in a complex process to determine offspring outcome [7]. Accordingly, rather than a simple causal chain, the image of a spider's web has been considered most appropriate for describing the causal context of FASD [8].

Causal inference, the science of inferring the presence and magnitude of cause–effect relationships from data, is a central aim of epidemiology [9, 10]. However, much of the existing FASD literature simply lists risk factors and reports associations with little consideration of the underlying causal structure. The term ‘risk factor’ obscures the distinction between a predictor variable and a cause [11]. While knowledge of predictor variables is important for identifying who is most at risk of FASD and for targeting interventions, causal knowledge is important for identifying

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effective mechanisms for prevention and intervention programmes [12].

Randomised controlled trials can be used to estimate causal effects. However, for many public health issues, including prenatal alcohol exposure (PAE), randomisation of exposure is unethical and/or unfeasible and, therefore, it is necessary to rely on observational data. Measures of (conditional) association from observational designs can be used to estimate causal effects if conditional exchangeability is created by appropriate control of bias, such as adjustment for confounders [11]. Causal diagrams, known as directed acyclic graphs (DAGs), are gaining popularity as a gold standard method for supporting causal inference and reducing bias in epidemiological studies [13]. Judea Pearl devised the unifying framework that provided this graphical method and formal language for causal inference [14]. Pearl reasoned that the combination of observed data plus causal knowledge allows individuals to move beyond the realm of statistical association to that of causality. DAGs provide a tool for explicitly characterising assumptions about the causal relationships between exposures, covariates, and outcomes [15]. The graphical rules that underpin the interpretation of causal DAGs have a well-established mathematical basis [14]. They provide a systematic method for identifying which variables should be controlled for in the analysis, and which should not, to minimise bias in effect estimates, on the basis of the assumptions encoded in the DAG [14]. In scenarios where DAGs contain a large number of variables they become less clear as visual overviews of the causal context, but maintain their utility as a theory driven approach to statistical modelling strategies. In contrast to data-driven approaches, it is the hypothesised causal relationships depicted by the DAG, rather than measures of statistical significance that can be used to guide variable selection in subsequent quantitative analyses [16]. A detailed description of DAG language and theory is provided in Online Resource 1. In this review, we conduct a narrative literature synthesis and present a DAG to describe the hypothesised causal structure of the variables that are involved in the pathways to FASD. We also provide a worked example of how the DAG can be used to support statistical modelling strategies.

Method

Literature search

We searched Medline from inception to 2nd March 2016 for existing systematic reviews of FASD risk factors using combinations of medical search headings (MeSH) and free text search terms for FASD, risk factors and reviews, as described in Online Resource 2. This search produced two references, one of which, by Esper et al. [17], was relevant

to the aims of this review. To obtain more information about possible causal structures, we searched the full text articles of the included studies from this review and conducted separate searches for each risk factor in Medline. In each search, we combined search terms for FASD and the relevant risk factor (see Online Resource 2 for example search on FASD and stress). Supplementary sources were searched to identify any risk factors that were not identified in the initial review and to provide further information on identified risk factors. Sources included: the Infant Feeding Survey [18–20], publications from the Millennium Cohort Study [21] and ALSPAC [22], the National Organization on Fetal Alcohol Syndrome and EUFASD newsletters, a search of study reference lists, Research Gate and FASD conference abstracts [23–25]. Supplementary searches were concluded on the 22nd December 2017.

Evidence synthesis

To determine the most plausible structure for the aetiology of FASD, we used informal triangulation methods to evaluate the evidence from the literature search. Unlike systematic reviews, which seek to compare results from studies that are relatively homogenous, triangulation seeks to compare evidence from studies from a diverse range of approaches. The advantage of triangulation is that any biases are assumed to differ across the diverse study types. This increases confidence in causal inferences if similar effect estimates are obtained [26].

DAG construction

We used the DAGitty platform [27] to draw and interpret a DAG based on the evidence synthesis. DAGitty code is provided in Online Resource 3.

Results

The DAG (Fig. 1) provides a visual description of the hypothesised aetiological context of FASD, based on the evidence synthesis.

In this section, we present the narrative synthesis of evidence that supports the inclusion of factors in the DAG, and their position, followed by a worked example of how the DAG can be used to inform statistical modelling strategies. In Online Resource 4, we provide a more detailed description of the groupings of variables that were derived following the evidence synthesis, to enable further comparison of the literature review with the causal (and non-causal) relationships depicted in the DAG.

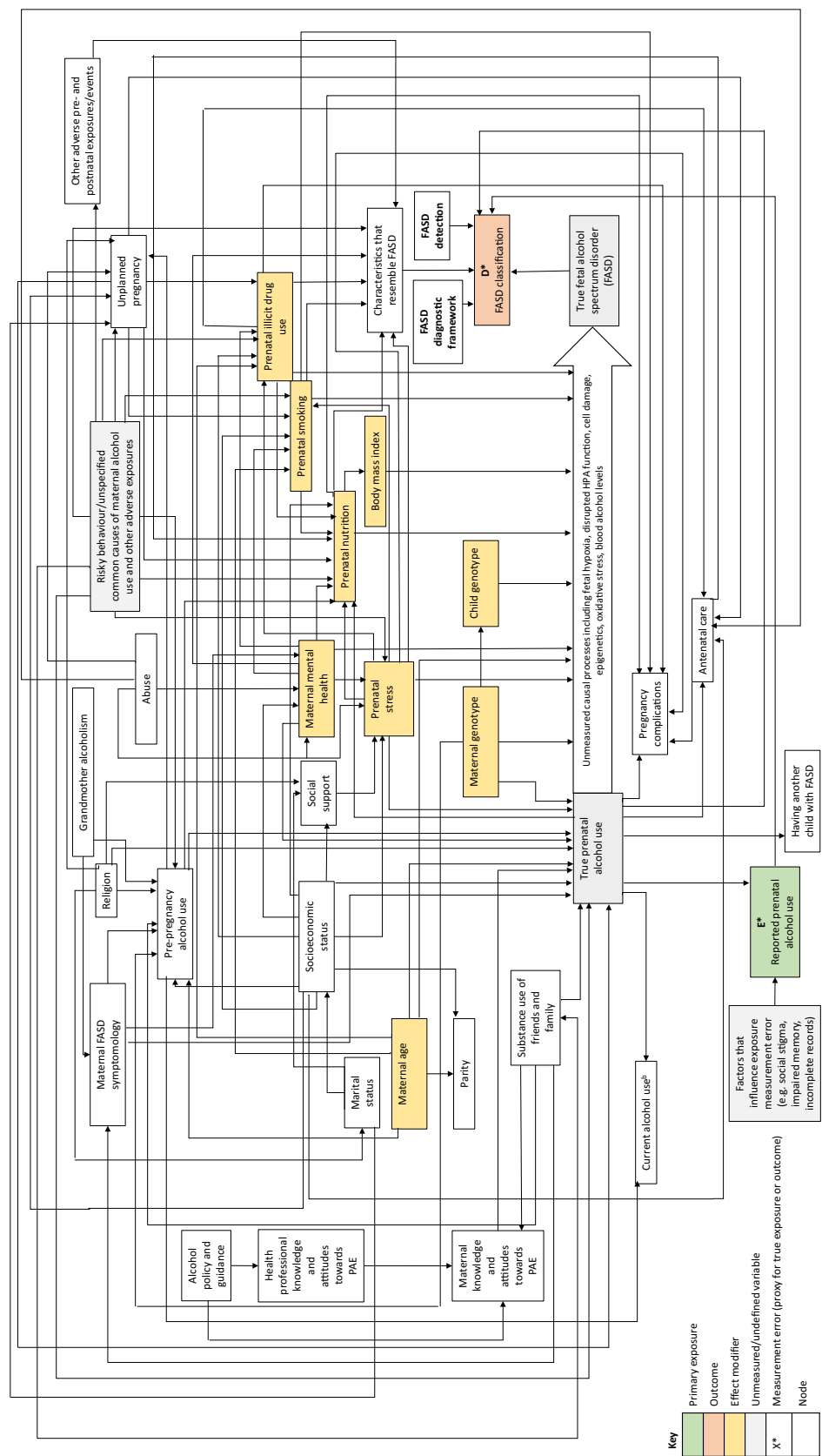


Fig. 1 Directed acyclic graph (DAG) depicting the hypothesised causal pathways to FASD. Note: evidence of prenatal alcohol exposure is required to consider a diagnosis of FASD. **a** Rural residence may be Rural residence may be a risk factor that is particular to farming communities in South Africa, due to normative binge pattern drinking behaviour and adverse social conditions, **b** Having another child with FASD and current alcohol use are descendants of prenatal alcohol use and descendants of all factors that influence alcohol use before and during pregnancy. These connecting arcs have not been depicted in the DAG for clarity of presentation

Patterns of maternal alcohol use (prenatal alcohol exposure)

During pregnancy, alcohol consumed by the mother passes freely through the placenta and within 1 h the level of alcohol within the foetal bloodstream approximates that of the mother [28]. For simplicity, we use term prenatal alcohol exposure (PAE) to refer to maternal alcohol use, although it is important to note that maternal alcohol use is just one element of foetal alcohol exposure, which is also influenced by maternal and infant metabolism and other modifying factors, described in this review.

The impact of PAE varies according to the dose, frequency and timing of exposure. However, residual confounding, measurement error and individual variability across a vast range of covariates complicate efforts to determine what pattern of maternal alcohol use will lead to FASD in an individual case. Nevertheless, on average, binge and heavy chronic patterns of maternal alcohol use are most likely to result in FASD [29–34]. Evidence on the effects of low to moderate PAE on developmental outcomes is limited and inconsistent, ranging from evidence of harm, to no effect, to evidence of slight benefit [35–44]. For example, Kelly et al. found that 3-year-old boys who were born to mothers who reported drinking no more than one to two units of alcohol per week or per occasion during pregnancy had a lower risk of hyperactivity and conduct problems than those born to abstainers [40]. Negative control studies that compare the strength of association for maternal and paternal exposures have also been used to investigate the causal effects of low to moderate PAE, but did not find evidence of intrauterine effects on child IQ or head circumference [41, 42]. In contrast, Mendelian randomisation studies have offered evidence that low to moderate PAE can cause persistent conduct problems and adversely affect cognitive and academic outcomes [37, 38, 43]. Despite inconsistencies in the evidence, Mendelian randomisation studies provide stronger causal evidence than traditional observational studies that low to moderate alcohol use can cause adverse developmental outcomes. They suggest that the apparent null or protective effects of low to moderate PAE are likely to be due to residual confounding, owing to the socioeconomic patterning of prenatal alcohol use [36, 37, 44].

Alcohol use before pregnancy

Mothers of children with FASD are more likely to drink at high levels before pregnancy, to have had longer ‘drinking careers’ (i.e. more years of drinking alcohol), and to have a history of alcohol abuse, relative to controls [30, 32, 33, 45]. Chronic alcohol use impairs the functioning of alcohol metabolising enzymes and can lead to malnutrition due to

reduced intake and absorption of key nutrients, thus increasing FASD risk [5, 46–49].

In the UK, up to 91% of women aged 16–45 report drinking alcohol and excessive consumption is common [50, 51]. Few women follow guidance for prenatal alcohol use when planning a pregnancy [52] and alcohol use increases the risk of unplanned pregnancy [53–56]. Therefore, alcohol use prior to pregnancy is a significant risk factor for FASD.

Postnatal alcohol use

Mothers of children with FASD drink more heavily than controls postnatally [33, 57–65]. Of course, heavy postnatal alcohol use cannot cause FASD among children who have already been born. It can, however, indicate a continuing pattern of heavy alcohol use and serve as a risk marker for previous and future alcohol-exposed pregnancies. Heavy postnatal alcohol consumption may be a useful proxy for PAE. Studies from the USA and Italy found that self-reported prenatal alcohol use was not consistently different between mothers of children with FASD and controls, but current consumption was higher [34, 63, 64]. In contrast, studies in the Western Cape of South Africa (where maternal self-report is believed to be more reliable, due to normative binge drinking patterns and higher levels of PAE) show consistently higher levels of self-reported PAE and current consumption among mothers of children with FASD [33, 57–60, 62]. Therefore, postnatal drinking patterns may be particularly useful as a risk marker for previous PAE and for future FASD risk in populations that are susceptible to underreporting of PAE.

Smoking during pregnancy

Prenatal cigarette smoking is more common among mothers of children with FASD than those without [17, 58]. Smoking and PAE may interact synergistically to increase the risk of FASD-related outcomes including low birth weight [66]. Proposed biologic mechanisms for the interaction between tobacco and alcohol include common effects on nutrient availability, oxidative stress and vasoconstriction of the placenta and umbilical cord, which can lead to hypoxia and prolonged uterine exposure to ethanol [5, 66, 67]. In addition to its interactive effect with PAE, prenatal smoking is independently associated with reduced foetal growth, low birth-weight and cognitive and behavioural impairment [68–75]. Evidence suggests that the impact of smoking on decreased birth weight is up to three times greater than that of PAE [68, 76]. Therefore, prenatal tobacco exposure can lead to characteristics that resemble FASD, even in the absence of alcohol exposure. Prenatal smoking is more common among mothers with an unplanned pregnancy, mothers with other forms of substance use, mothers who report prenatal stress,

younger mothers, and mothers of lower socioeconomic status (SES) [19, 69, 73, 77].

Illicit drug use during pregnancy

Prenatal illicit drug use is more prevalent among mothers of children with FASD [30, 78] and it can lead to similar physical, cognitive and behavioural impairments that are relevant to FASD diagnosis [79, 80]. Cocaine, opiates and amphetamines have been found to increase the risk of intrauterine growth restriction, low birth weight, small head circumference and congenital anomalies [72, 79–81]. However, the effect of illicit substance exposure on birthweight and foetal growth is thought to be less severe and persistent than that of PAE and prenatal smoking [68, 71]. Children with prenatal illicit substance exposure may show catch-up growth [82] and effects are significantly attenuated following adjustment for adverse social factors [83]. Evidence on the effect of prenatal marijuana exposure on growth outcomes has been inconsistent [68, 71, 84]. However, marijuana use may lead to subtle impairments in cognitive and motor skills in childhood and adolescence [85–87]. In a mouse model study, synthetic cannabinoids were found to interact with ethanol to increase the prevalence of ocular defects [88].

Prenatal cocaine exposure may impair attention, speech and language development [89–91]. Opiate exposure can lead to neonatal abstinence syndrome, which is characterised by abnormal arousal and irritability [80, 81]. Prenatal amphetamine exposure has been linked to smaller subcortical volume, externalising behaviour, and cognitive deficits [92–94]. It is unclear whether illicit drugs modify the effects of PAE [83]; however, prenatal illicit drug exposure and PAE share common biological mechanisms of harm including restricted blood flow to the foetus and altered neuroendocrine regulation [79, 95].

Prenatal illicit drug use is associated with a range of social and psychological factors including low socioeconomic status (SES), stress, mental health problems, abuse and low social support [79, 83, 96]. Although maternal drug use may contribute to subsequent adverse social and psychological outcomes, such factors are primarily perceived as preceding factors that increase the likelihood of drug use [83]. Illicit drug use increases the risk of inadequate prenatal care, pregnancy complications, and poor nutrition and is more common among older women and those with an unplanned pregnancy [79, 83, 95, 97].

Prenatal nutrition

Prenatal nutrition features at several points in the causal context of FASD. Nutrition modifies the impact of PAE on FASD, influences maternal BMI, and is influenced by maternal substance use, maternal mental health, stress,

antenatal care, whether pregnancy was planned or not, and SES [5, 98–101]. Greater consumption of processed foods has been found to be associated with heavier alcohol intake and healthier diets with low-to-moderate alcohol intake during pregnancy [102]. These associations may be due to latent factors such as tendencies towards healthy or unhealthy lifestyle behaviours (depicted as the ‘risky behaviour’ node in the DAG). Among children with PAE, lower calorific intake has been found to increase the risk of FASD, while evidence from animal studies suggests that specific nutrients (including vitamin A, docosahexaenoic acid, folate, zinc, choline, vitamin E, selenium, riboflavin, calcium, docosapentaenoic acid, zinc, B-vitamins, iron and protein) may reduce the risk of FASD-relevant outcomes including physical malformations, growth deficiency, behavioural regulation and memory [98, 99, 103–106]. During pregnancy, mothers of children with FASD report a lower intake of key nutrients and report being hungry more often than controls [59, 107]. Deficient nutrient intake does not, however, fully explain increased risk for FASD. Even with equivalent dietary intake, alcohol-exposed rats weigh less and produce offspring with poorer outcomes than unexposed rats [104, 108]. Alcohol competes with nutrients that are essential for foetal development due to shared metabolic pathways [109, 110] and can lead to impaired placental blood flow and nutrient transportation [49, 98, 111, 112]. Nutritional supplementation has been found to attenuate FASD symptomology in some animal models [98]. Results in human studies are limited and inconsistent [113–115].

Socioeconomic status (SES)

Indicators of SES including low maternal education and income have been identified as risk factors for FASD [17, 58]. Perhaps counterintuitively in light of these results, the UK Infant Feeding Survey has consistently found that women within higher social classes are more likely to drink during pregnancy than those from lower social classes [18, 19, 116, 117]. UK-based cohort studies have echoed these results, showing that women who drink in pregnancy are more highly educated, less likely to live in deprived areas, and more likely to be employed than abstainers [37, 118, 119]. Although high SES is associated with an increased risk of prenatal alcohol use, mothers of low SES who do drink during pregnancy are more likely to do so in a binge pattern [37]. As well as differences in the social patterning of alcohol use, children born to high SES mothers may be relatively protected against the harms of PAE due to factors associated with social advantage [39]. These factors are included in the DAG as consequences of SES and, among others, include differences in social support, stress, prenatal

nutrition and prenatal smoking, which could offer potential targets for intervention.

Based on the available evidence, it is hypothesised that SES is associated with FASD via the causal pathways proposed by Abel et al. [5], in which low SES contributes to FASD through its influence on drinking patterns, stress, mental health, illicit substance use, smoking and nutrition.

Maternal age

Several studies have found that older maternal age is associated with an increased risk of FASD [17, 58]. Older mothers are more likely to drink during pregnancy than younger mothers, although binge drinking is more common among younger mothers [18, 19, 116–118]. Blood alcohol concentration (BAC) per unit dose increases with age, leading to higher levels of exposure per unit consumed among the offspring of older mothers [120–123]. Higher BACs may be partly explained by age-related changes in body composition including an increased body-fat-to-water ratio among older individuals [120, 122–124]. Some studies have also found differences in rates of ethanol metabolism among older participants, although results are mixed [121–123, 125–130]. Chronic alcohol exposure, which is associated with maternal age, can impair nutrient transportation [112, 131]. Thus, maternal age is proposed to influence the risk of FASD through differential patterns of PAE, BAC and effects on nutrient availability.

Marital status

Mothers of children with FASD are less likely to be married and more likely to be cohabiting with a partner than controls [17]. Existing studies do not offer an explanation as to the causal basis of this relationship; however, it is possible that marriage may protect against FASD by offering a form of social support. It may also indicate fewer relationship problems, which have been cited as a source of prenatal stress and predictor of PAE among mothers of children with FASD. In addition, marriage is associated with higher SES and lower risk of unplanned pregnancy, which predict a lower risk of FASD.

Religion

Esper et al. concluded that ‘less religious’ women had an increased risk of having a child with FASD [17]. However, evidence is mixed. Three South African studies found that mothers of children with FASD reported a lower frequency of church attendance and prayer than controls [33, 59, 62]. Conversely, studies in Italy found that women categorised as more religious were more likely to have a child with FASD than those classed as less religious [64, 65]. Other studies

have found no significant differences in the religious practices of mothers of children with FASD and those without [132]. These studies do not provide any insight into possible causal relationships between religion and FASD. However, the extent to which religion may protect against, or be a risk factor for, FASD is likely to depend on its association with more proximal risk factors for FASD, such as alcohol use, unplanned pregnancy and social support. For example, religions differ in their stance towards alcohol consumption. The Islamic faith promotes abstinence from alcohol and abstinence is high among Muslims [133]. The prevalence of FASD is 50 times lower than the global average in the World Health Organisation (WHO) Eastern Mediterranean Region, where the population is predominantly Muslim [6]. In contrast, wine is part of Communion in the Catholic faith and abstinence is much less common among Catholics [133]. Astley et al. found that mothers of children with FAS were more likely to become abstinent in the future if they reported a religious affiliation and more satisfactory support networks [134]. Finer et al. found that religion was associated with a reduced risk of unplanned pregnancy [135]. Therefore, religion may protect against FASD if the faith promotes abstinence from alcohol, or drinking in moderation, reduces the risk of unplanned pregnancy, and offers social support.

Parity

Parity is higher among mothers of children with FASD, relative to controls [17, 58]. Some authors have suggested that higher parity could increase susceptibility to alcohol teratogenicity due to greater levels of uterine collagen and elastin, which reduce blood flow and contribute to foetal hypoxia [5]. However, experimental studies suggest that it is maternal age, rather than parity that modifies the effect of PAE on offspring outcomes. When rats of the same age, but different parity, are exposed to equivalent levels of alcohol, the number of birth defects is comparable across groups. In contrast, older rats are more likely to produce offspring with birth defects following PAE than younger rats, when parity is equivalent [136, 137].

Pregnancy complications

Mothers of children with FASD report more complications including preterm delivery, foetal distress, miscarriage, stillbirth and admission to special care baby units [31, 33, 138, 139]. Pre- and perinatal complications are an effect of PAE and may serve as a marker of exposure to factors associated with increased risk of FASD. Complications during pregnancy and delivery have also been linked to other exposures including prenatal smoking, prenatal illicit drug use, poor nutrition and prenatal stress [31, 33, 95, 138–143]. The risk of pregnancy complications may be mitigated by

adherence to antenatal care recommendations and monitoring [97, 144].

Antenatal care

Compared to controls, mothers of children with FASD are less likely to have received antenatal care, more likely to have accessed care late in pregnancy and more likely to have attended fewer antenatal appointments [30, 31, 78, 138, 139]. Women who misuse substances may be likely to access prenatal care due to fear about negative staff attitudes, the involvement of children's services, and feelings of guilt [97]. As well as influencing uptake of antenatal care, prenatal substance use may be influenced by antenatal care. For example, mothers accessing antenatal care via the National Health Service (NHS) are provided with information about the risks of prenatal substance use and support organisations [145]. In the USA, pregnant women who have health insurance are approximately 50% less likely to have consumed alcohol in the last month, further suggesting that antenatal care can influence PAE (although this relationship may also be due to the association between PAE and SES) [146]. Therefore, there is a time-dependent causal relationship between PAE [and similarly other types of prenatal substance use (e.g. smoking, illicit drug use)] and antenatal care. For example, alcohol use during very early pregnancy (time 1) may affect attendance at the first antenatal booking appointment (at 8–12 weeks in the NHS), which may then affect alcohol use in the second trimester (time 2) and so on. As it is not possible to have feedback loops within DAGs, the full sequence can be conceptualised as a series of time-dependent factors, for example: *substance use before pregnancy* → *prenatal alcohol use at time 1* → *attendance at antenatal care* → *prenatal alcohol use at time 2*. To avoid over-cluttering the DAG, we depicted antenatal care as a consequence of prenatal substance use (time 1 relationship only).

Unplanned pregnancy

Worldwide, 40% of pregnancies are unplanned [147], ranging from 16% in the UK [56], 35% in Africa, and 51% in North America [147]. Unplanned pregnancy is a risk factor for FASD. Among a sample of mothers of children with foetal alcohol syndrome (FAS) in the USA, 73% of live births were unplanned [134]. Unplanned pregnancy is more common among women who drink regularly and/or binge drink [53–56] and binge drinking is associated with inadequate methods of contraception [148]. Therefore, the risk of unintended PAE during the periconceptual period is high. Women who have an unplanned pregnancy are less likely than those with a planned pregnancy to follow advice for prenatal lifestyle behaviours including alcohol use, smoking

and diet [52, 149, 150]. A qualitative study of pregnant women who attended alcohol establishments in South Africa suggested that some women with unplanned pregnancies continued to drink because they did not feel a connection with their unborn baby, and some women reported drinking in an attempt to abort the foetus [151].

Other factors associated with an increased risk of unplanned pregnancy include low SES, single marital status, exposure to intimate partner violence, smoking, illicit drug use and younger maternal age, while religion is associated with a decreased risk [53, 54, 56, 134, 135, 152]. Some of these factors may be causal and others may be risk markers for unplanned pregnancy due to their association with other causal factors. For example, low SES may have a causal relationship with unplanned pregnancy, as women may be less likely to commit limited financial resources to contraceptives. Studies conducted in the USA show that unplanned pregnancy is more common among poorer women [135] and in one study 43% of women who gave birth to a child with FAS reported that they could not afford contraception [134]. Conversely, socioeconomic status was not found to be associated with unplanned pregnancy in a UK study, where contraception is available for free [56]. Intimate partner violence may be causally associated with unplanned pregnancy due to an increased risk of sexual coercion, and sabotage of contraception [152, 153]. Substance use before pregnancy may be causally associated with unplanned pregnancy, as it increases the likelihood of not using contraception [148, 154]. Further consequences of unplanned pregnancy include late prenatal care and complications during pregnancy [53–55, 135, 155].

Prenatal stress

Mothers of children with FASD are more likely to report that pregnancy was a particularly stressful time and to have experienced stressful life events, including abuse and interpersonal violence [8, 17]. Qualitative evidence suggests that some mothers may use alcohol to alleviate stress during pregnancy [62, 134, 151]. Prenatal stress has been found to predict co-occurrence of PAE, prenatal smoking, illicit drug use, and poor nutrition [77, 83]. It is important to acknowledge that substance use may also cause prenatal stress; however, in the literature, stress is typically thought to precede substance use [33]. As well as influencing drinking behaviour, prenatal stress may exacerbate the teratogenic effects of alcohol [156]. In a Ukrainian study, prenatal depression and PAE jointly influenced neurodevelopmental outcomes in infants. This effect may have been partially mediated through prenatal stress [16]. Reviews of animal studies have concluded that PAE and stress operate synergistically to impair developmental outcomes [7]. Primate studies have found that concurrent exposure to prenatal stressors

exacerbate alcohol-induced behavioural and neurodevelopmental impairments [157, 158]. However, evidence is inconsistent and not all studies have found an interaction between PAE and stress in producing outcomes relevant to FASD symptomatology, possibly as a result of small sample size [159–161].

Several biological mechanisms have been proposed to account for observed interactions between PAE and stress in FASD. One hypothesis is that PAE and prenatal stress produce lasting changes in the functioning of the foetal hypothalamic–pituitary–adrenal (HPA) axis, which is involved in the stress response. This effect is heightened in the presence of both PAE and stress, relative to their individual contribution [162–164]. Endocrine dysregulation may contribute to the risk of FASD by influencing behavioural, cognitive and emotional functioning [157, 163]. Dual exposure may also contribute to foetal hypoxia by restricting uterine blood flow and suppressing foetal breathing. Hypoxia promotes cell damage, which may lead to midfacial abnormalities [156] and can be particularly damaging in areas such as the hippocampus and cerebellum which are involved in attention, motor function and learning [5, 157]. Prenatal stress has been independently linked to adverse child outcomes and congenital anomalies and, therefore, may produce symptoms that resemble FASD [156, 165–168].

Maternal mental health

Mental health disorders are common among mothers of children with FASD [17, 32, 134]. Among a clinic-based sample of 80 mothers of children with FAS in the USA, 96% had one or more mental health disorders [134]. The mechanisms that link prenatal mental health to child outcomes are poorly understood; however, effects are thought to be facilitated primarily via increased stress hormone circulation and altered HPA functioning, as described in the previous section [169–171]. Bandoli et al. found that unmedicated maternal depression and PAE interacted to predict poorer outcomes on the Bayley Scales of Infant Development (BSID) at ages 6 and 12 months, while maternal depression, alone, was not independently associated with neurodevelopmental outcomes [16]. Santucci et al. also failed to find an association between prenatal depression and BSID scores [172]. Other studies have found an independent association between prenatal depression symptoms and poorer emotional–behavioural and cognitive outcomes in children up to age eight [100, 101]. These effects were thought to be partially mediated through an unhealthy prenatal diet. Overall, results are inconsistent with regard to the independent influence of prenatal mental health on FASD-related symptomatology. Following a review of the evidence, Waters et al. concluded that, with the exception of conduct problems, prenatal depression does not appear to independently

influence child neurodevelopmental outcomes [170]. Therefore, associations between prenatal mental health and FASD are thought to be largely mediated by the prenatal stress response rather than mental health itself.

In addition to its interaction with PAE, maternal mental health may influence drinking behaviour due to the use of alcohol for self-medication [151, 173], as depression often precedes alcohol use disorder [174]. Mothers who have a child with FAS and subsequently receive mental health treatment are more likely to report abstinence, suggesting a promising target for FASD prevention [134]. Maternal mental health issues may also affect foetal development by increasing the risk of other adverse exposures including illicit substance use, smoking and poor prenatal nutrition [83, 100, 101, 175].

Social support in pregnancy

Social support during pregnancy is associated with reduced alcohol intake in European and American samples [176, 177]. Social support may protect against PAE by attenuating the impact of stressors and reducing the likelihood that alcohol will be used as a coping strategy. Mothers of children with FASD are more likely to achieve abstinence in the future if they report having a large, satisfactory support network [134]. However, the beneficial effects of social support on alcohol use may be less apparent among women in poverty and within subcultures that normalise drinking in pregnancy [151, 178].

Abuse

FASD is more common among children born to women who have experienced childhood physical or sexual abuse and/or intimate partner violence [17, 32, 33, 134]. Substances including alcohol may be used as a self-medication strategy to alleviate stress and mental health symptoms among those who have experienced abuse [179]. Abuse influences whether mothers reduce their alcohol intake following pregnancy recognition. 72% of mothers of children with FAS reported that they did not want to reduce their alcohol use because they were in an abusive relationship [134]. Abuse may also influence risk of FASD by acting as a barrier to adequate antenatal care. Women experiencing domestic abuse may be prevented from accessing antenatal care or may be reluctant to access care due to concerns that disclosure of abuse would make the situation worse, or lead to involvement of child protection services [97].

Maternal physical characteristics

Lower maternal height, weight and BMI have been found to consistently predict FASD in studies in South Africa [33,

58–61, 132]. Studies conducted in Italy and the USA have been less consistent with regard to BMI, but have found that mothers of children with FASD tend to be shorter or weigh less than those without FASD [34, 63, 78, 99]. Maternal physical characteristics influence the distribution of alcohol after it is consumed. As alcohol is distributed in body water, blood alcohol concentrations (BACs) tend to be higher in smaller women [180, 181]. As well as influencing BACs, higher maternal weight and BMI may indicate adequate nutrition. Although higher BMI may protect against FASD, it is important to note that maternal obesity is associated with a range of adverse outcomes including gestational diabetes mellitus, induction of labour and preterm delivery [182].

Maternal FASD symptomology

Mothers of children with FASD are more likely to have symptoms of FASD themselves, including cognitive impairment and small head circumference [32, 58, 59]. Up to 94% of individuals with FASD have comorbid mental health disorders [183], including conduct disorder (91%), ADHD (51%), and depression (35%) [184]. In turn, impaired mental health increases the risk of PAE. 55% of individuals with FASD experience drug or alcohol dependence later in life [184], thus increasing the risk of FASD in subsequent generations.

Knowledge and attitudes towards PAE and FASD

Public awareness of the risks of PAE is low. Inconsistencies in guidance and mixed advice from health professionals are likely to contribute this lack of awareness [185]. A UK study, published in 2015, found that 40% of participants did not know the government guidance on PAE. Most participants (71%) also said that government guidance on PAE was unclear and some said that this lack of clarity was likely to lead to messages being disregarded [186]. Health professionals have been found to give mixed advice to women about PAE. The UK Infant Feeding Survey 2010 reported that 30% of expectant mothers were not given any information about PAE. Among women who received advice, 36% were given information on reducing their intake and 29% on stopping drinking [19]. In the absence of clear evidence about a 'safe' threshold for PAE, opinions can be polarised. Some groups endorse a 'no alcohol no risk' message, while others warn against the 'policing of pregnancy' and suggest that women should be free to make an educated choice about whether they drink when trying to conceive and during pregnancy [187, 188]. Behaviour and attitudes towards PAE differ according to social norms and may be influenced by national public health policy [189].

Alcohol use of friends and family

Mothers of children with FASD report higher levels of alcohol consumption by their partner, family and friends [17, 34]. Ceccanti et al. found that alcohol problems in the family increased the likelihood of having a child with FASD by nine times [63]. Alcohol use by friends and family may impact on PAE in various ways. First, the drinking behaviour of those in close social networks may represent the norms within that context. For example, a binge pattern of drinking may be viewed as less problematic in some communities in South Africa where heavy episodic alcohol use is commonplace [132]. Second, some women may feel coerced into drinking before and during pregnancy as a result of the behaviour of friends and family. In a study of mothers of children with FAS, Astley et al. reported that 36% of women said that they did not want to reduce their prenatal alcohol intake because their partner did not want them to, and 20% because their family and friends did not want them to [134]. Strong correlations between maternal substance use and the substance use of friends and family could also be due to processes of self-selection, in which individuals pick companions who are similar to themselves and who support their behaviour [190]. In the DAG, we represented this mechanism via the unspecified 'risky behaviour' node that influences both maternal substance use and choice of social network. Finally, as described above, mothers of children with FASD are more likely to have symptoms of FASD themselves and to report that the maternal grandmother has a history of alcohol problems [32, 59]. This raises the possibility of intergenerational transmission of FASD, a phenomenon that has received support via controlled animal studies [191]. Heavy alcohol use by the maternal grandmother could indicate the presence of a risk genotype for heavy alcohol use [192], could result in epigenetic changes that increase the risk of heavy alcohol use in later generations [191] and could provide a model of problematic alcohol use that is adopted by offspring via social learning [193]. Recent evidence from animal studies suggests that paternal alcohol consumption could influence the epigenetics of sperm DNA by influencing methylation patterns in sites that are important to developmental outcomes [194]. Paternal alcohol use has been associated with FASD symptomology including low birth weight, reduced brain size, microcephaly, impaired learning and hyperresponsiveness [42, 195], although results have been inconsistent [196].

Having another child with FASD

An early study, published in 1979, found that 70% of children with FAS had a sibling with confirmed or suspected FAS [197]. In the FAS Surveillance Network, between 9 and 29% of mothers have another child with FASD [30]. Having

another child with FASD is also a strong predictor of subsequent alcohol-exposed pregnancies [30, 31, 197, 198]. In a cross-sectional study of mothers of children with FAS, 80% subsequently had an unplanned pregnancy, of which 75% were alcohol exposed [134]. In the absence of intervention, women who are at risk of having another child with FASD may exist within the same causal context as that which surrounded their first affected pregnancy. Thus, identifying mothers who have had a child with FASD is an important focus for targeted prevention [198].

Genetics

Genetic factors modify susceptibility to alcohol-related harm [192, 199–201]. Dizygotic twins have differential susceptibility to FASD, while monozygotic twins have high levels of concordance [202–205], different strains of mice have diverse outcomes according to their genotype [206, 207] and particular genetic variants are more common among alcohol-exposed children who develop FASD, compared to those who do not [208, 209]. A range of genes have been investigated in animal models of FASD, including aldehyde dehydrogenase (ALDH), *Fancd2*, *Cdon*, *Gli2*, *Shh*, *Nos1*, *PDGFRA*, *hinf1*, *foxi1*, *mars*, *plk1* and *vangl2*; however, these genes are yet to be explored in human studies [201]. In humans, polymorphisms of alcohol dehydrogenase (ADH) genes have been the primary focus of investigation [199–201]. ADH enzymes oxidise ethanol to acetaldehyde and account for up to 95% of alcohol metabolism. ALDH and CYPE2E1 also influence ethanol metabolism in humans; however, their role in FASD susceptibility is yet to be established [200, 208]. Polymorphisms at the ADH1B locus produce enzymes that affect the rate of ethanol clearance. In populations of European ancestry, the slow-metabolising allele, ADH1B*1, is the typical variant and occurs in approximately 95% of individuals. The rare ADH1B*2 and ADH1B*3 alleles convert ethanol to acetaldehyde 75–88 times faster than ADH1B*1 [210]. Maternal and infant ADH1B genotype has been found to influence risk of FASD as, with the exception of one study [211], fast-metabolising alleles have been associated with a reduced risk of FASD symptomology following PAE [208, 212–215].

Lewis et al. explored the impact of ADH polymorphisms on children's IQ following PAE [38]. Rare variants of four child single nucleotide polymorphisms (SNPs; ADH7 rs284779, ADH1B rs4147536, ADH1A rs975833 and ADH1A rs2866151; herein referred to as the SNP set) were negatively associated with IQ at age eight for children with low to moderate alcohol exposure in utero (1–6 units per week). These rare variants were hypothesised to be associated with slower metabolism, leading to relatively increased alcohol exposure and teratogenicity [38, 216]. However, a study of in vivo alcohol metabolism failed to show that these

SNPs influenced blood or breath alcohol concentrations [217]. Within this study, another SNP, ADH4 rs4148884, had divergent effects. The rare allele was associated with decreased offspring IQ when present in the maternal genotype, but increased IQ when present in the child's genotype. These SNPs were not associated with IQ among children of non-drinking mothers, suggesting that genotype acted as an effect modifier following maternal alcohol intake.

As well as influencing alcohol metabolism, genotype may influence drinking behaviour and, hence, the interest in ADH variants as instrumental variables in Mendelian randomisation studies [12]. Patterns of alcohol consumption tend to run in families and several genes have been found to contribute to risk of alcoholism [192, 196]. ADH1B has been widely studied and research shows that individuals with the rare allele consume less alcohol than those with the typical allele and have a reduced risk of alcoholism [218–221]. In pregnancy, mothers with the rare ADH1B allele have been found to consume significantly less alcohol before pregnancy and to be 50% less likely to binge drink during pregnancy [222]. Therefore, genotype may influence the risk of FASD through its influence on both alcohol metabolism and drinking behaviour [37].

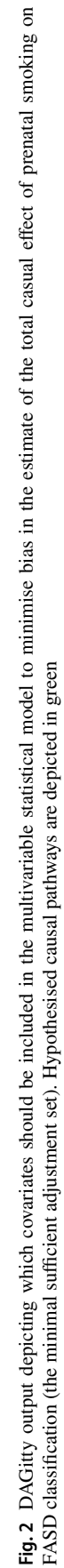
Using the DAG to support causal inferences and statistical analyses

To demonstrate how the DAG presented in this review can be used to clarify the causal pathways to FASD and to support statistical modelling strategies, we present a worked example using prenatal smoking as the risk factor of interest. We replicated the causal structure depicted in Fig. 1 in the DAGitty platform [27]. In all circumstances, there must have been prenatal alcohol exposure for there to be true FASD. The representation of the DAG that includes smoking as the key co-exposure in DAGitty is shown in Fig. 2.

There were six hypothesised causal pathways that accounted for the total causal effect of prenatal smoking on FASD classification among children with PAE.

These were

1. Prenatal smoking → 'true' FASD (unobserved) → FASD classification
2. Prenatal smoking → prenatal nutrition → 'true' FASD (unobserved) → FASD classification
3. Prenatal smoking → prenatal nutrition → BMI → 'true' FASD (unobserved) → FASD classification
4. Prenatal smoking → characteristics that resemble FASD → FASD classification
5. Prenatal smoking → prenatal nutrition → characteristics that resemble FASD → FASD classification
6. Prenatal smoking → prenatal nutrition → BMI → characteristics that resemble FASD → FASD classification



Pathways 1–3 describe participants who have a pattern of symptoms that met the criteria for FASD and whose symptoms were caused by PAE. These are the participants with ‘true FASD.’ In contrast, pathways 4–6 describe participants who have characteristics that resemble FASD, but whose presentation has been caused by factors other than alcohol exposure. In practice, and in the absence of the full facial phenotype for FASD, it is often difficult to determine whether the characteristics that contribute to a diagnosis were caused by prenatal alcohol exposure or other factors and this requires expert clinical judgement. All these pathways contribute to the total prevalence of FASD that is observed. Based on the graphical rules described in Online Resource 1 and operationalised by DAGitty, if the postulated DAG is correct, with no omitted common causes of any two nodes and no measurement error (these are strong assumptions), then an unbiased estimate of the total causal effect of prenatal smoking on FASD could be obtained by adjusting for the following variables in the analysis: maternal age at pregnancy, prenatal mental health, maternal ‘risky behaviour’ (e.g. personality trait variable), SES, prenatal stress and unplanned pregnancy. It is important to bear in mind that DAGitty provides, if one exists, a *minimally sufficient adjustment set* (i.e. the minimum set of variables that is required to eliminate bias). In this smoking example, the minimally sufficient adjustment set suggested by the DAG was maternal age, mental health, risky behaviour, SES, stress and unplanned pregnancy. The researcher interested in pursuing this could enter these variables into a multivariable statistical model to minimise bias in the estimate of the total causal effect of prenatal smoking on FASD classification. If the number of events is low, then limiting to the minimal adjustment set may be a good idea. In practice, if the data allow further adjustment without running into numerical problems or issues of finite sample bias, then adjusting for additional predictors of the outcome is advisable, as this will lead to a more precise estimate which is still unbiased. It is important to check, however, that the inclusion of these additional variables does not induce bias. To check that adjustment for an additional variable is not going to induce bias, one can add candidate variables to the adjustment set in DAGitty to see if this creates biasing pathways between the exposure and the outcome. Online Resource 1 provides further explanation of when adjustment can lead to bias.

Discussion

The aetiology of FASD is multifaceted and complex. The DAG that we have presented provides a summary of the distal and proximal factors that are proposed to causally influence FASD risk, as well as the factors that are proxies for causal factors or (non-causal) risk markers for FASD. Prior

to pregnancy, multiple distal factors influence pregnancy planning and lifestyle choices including pre-pregnancy alcohol use. These factors are proposed to influence subsequent prenatal alcohol exposure. Following prenatal exposure to alcohol, FASD risk is determined by a range of lifestyle, sociodemographic, maternal, social, gestational and genetic factors that mutually influence children’s outcomes. The use of causal diagram theory as the underpinning framework for this evidence synthesis allows us to move beyond discussion of association to make inferences about potential causal relationships between factors relevant to FASD. The principles of causal diagram theory can be applied to this DAG to inform study design and statistical modelling strategies for FASD research.

Strengths and limitations

Literature review and DAG methodology

The literature review and DAG that we have presented build upon existing reviews of risk factors for FASD [17, 99, 223] and provide an updated synthesis using the latest evidence. The use of DAG methodology represents a novel approach to the study of FASD and adds clarity to causal inferences in an area that has mostly been confined to discussions of association. As a visual representation, the DAG presents a unified summary of the current evidence on the aetiology of FASD.

Since the DAG has been constructed based on current subject-matter knowledge and our interpretation of plausible causal structures, it may be subject to change as new evidence emerges. This is not a limitation of the DAG approach, but rather reflects the realities of making causal inferences within a developing evidence base. In its current form, the DAG that we have presented may be a useful working template for researchers of FASD, who can use this tool to guide their analyses and update the causal structure of the DAG, as necessary. DAGitty code is provided in Online Resource 3 and can be copied and pasted into the DAGitty platform to replicate the DAG that we present in this review. Users can then use DAGitty to inform their own modelling strategy, based on this DAG and/or update the DAG based on their own hypotheses and emerging evidence.

The DAG may also help researchers at the design stage, by indicating which variables are important to measure. It is important to note that the causal inferences derived from the DAG rest on the assumption that the diagram is valid. The DAG is based on our interpretation of the evidence and, therefore, it is possible that given the same evidence other researchers may depict the relationships differently. Furthermore, the limitations inherent in the evidence base will necessarily apply to the results from this review and the DAG. Many proposed risk factors for FASD, such as prenatal

substance exposure and maternal stress, cannot be manipulated for ethical and practical reasons [224]. The evidence that we have used to construct the DAG was, therefore, based on experimental studies with animals and observational studies with humans. Animal studies have allowed the causal status of ethanol as a teratogen to be established [225] and have enabled causal conclusions about the influence of covariates such as stress and genetics on outcomes relevant to FASD [159, 207, 226]. Furthermore, in contrast to human studies, in which adverse exposures and health behaviours tend to co-occur, animal studies can isolate and evaluate the effects of specific exposures. However, animal models are imperfect substitutes for human studies for reasons including differences in alcohol metabolism, gestational processes, and their inability to replicate higher-level behavioural outcomes [7]. No single animal model has replicated all the attributes of FASD [225]. Observational studies of humans pose fewer concerns than animal studies in terms of exploring associations between a variety of co-occurring social and lifestyle factors and the full spectrum of FASD. However, this advantage is countered by the potential for bias due to the lack of experimental control. In general, observational studies are at risk of bias due to residual confounding, misclassification of the exposure and/or outcome, and differential loss to follow-up. In the evidence synthesis for the DAG, as well as studies with traditional observational designs, we included negative control and Mendelian randomisation studies. These studies are also subject to potential limitations. The contribution of paternal epigenetic factors to prenatal development in negative control studies remains to be established and effect estimates may be biased and imprecise in Mendelian randomisation studies if genetic instruments are weakly correlated with the exposure of interest and/or the instruments are invalid due to pleiotropy) [42, 221, 222, 227]. Nevertheless, the sources of bias differ for each approach and, under a triangulation method, the fact that the evidence from these different study designs points to a similar causal conclusion for many of the nodes of interest increases confidence in the causal hypotheses presented in the DAG [227, 228]. However, it may never be possible to determine whether the pathways suggested by the observational and animal studies represent the true causal pathways to FASD. Although this is a limitation of causal inference in general, compared to conventional statistical modelling strategies, approaches that make use of DAGs, when used sensibly, benefit from the increased transparency about causal assumptions and highlight likely remaining sources of bias.

The utility of DAGs in causal inference

Recently, there have been some criticisms about the gain in popularity of DAGs as tools to support causal inference. Kreiger and Davey Smith argue that DAGs have become

synonymous with ‘casual inference’ and that this unnecessarily narrows the scope of causal inquiry in epidemiology [228]. They assert that “robust causal inference...comprises a complex narrative, created by scientists appraising, from diverse perspectives, different strands of evidence produced by myriad methods. DAGs can of course be useful, but should not alone wag the causal tale” [228] (p. 1789). We agree, and this is why we have drawn upon a broad body of evidence to support the causal pathways depicted in the DAG. Daniel et al. have countered that DAGs do not purport to provide a substitute for careful consideration of the evidence base. Instead they should be a result of this [229]. Under this view, we would contend that the narrative synthesis that we have conducted is an example of the *approach* encouraged by the causal inference ‘school’ of Pearl et al. [14, 230, 231], while the DAG is the *tool* that summarises key causal assumptions and enables application of graphical rules to guide appropriate analyses and interpretation.

Finally, DAGs are nonparametric and thus often attract criticism for not formally allowing the concept of effect modification to be visualised. This is particularly relevant when trying to describe the aetiological context of FASD. In this context, while there is a sole necessary cause (alcohol), several effect modifiers may be present that influence whether PAE results in FASD. If one views the DAG solely as a means of deciding on an adjustment set, then there is no need to depict effect modification. However, if (as we have done here), the DAG is also used as a visual summary of existing evidence in this area, then it is useful to enhance the DAG with a depiction of effect modification. In the DAG (Fig. 1), we have followed Weinberg [232] and Thompson’s [233] suggestion by representing effect modification with an arrow that intersects the intermediate causal pathway from PAE to FASD, although other representations have been suggested [234, 235]. The representation of effect modification as an intersecting arrow in the direct pathway between PAE and FASD is purely for visual illustration. To enable analysis in the DAGitty platform, we directly connected the arrows from the proposed effect modifiers to the FASD outcome to allow application of the graphical rule algorithms [236].

Conclusions

The DAG presented in this review formalises and unifies current knowledge about the causal context of FASD. We believe that this DAG provides a useful synthesis of evidence for those interested in the aetiology of FASD and can be used as a tool to strengthen data collection and analysis strategies in studies of FASD risk factors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References

- British Medical Association (BMA) (2016) Alcohol and pregnancy: preventing and managing fetal alcohol spectrum disorders. BMA, London. <https://www.bma.org.uk/collective-voice/policy-and-research/public-and-population-health/alcohol/alcohol-and-pregnancy>. Accessed 23 May 2017
- Chudley AE, Conry J, Cook JL, Looock C, Rosales T, LeBlanc N (2005) Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. *CMAJ* 172:S1–S21. <https://doi.org/10.1503/cmaj.1040302>
- May PA, Chambers CD, Kalberg WO et al (2018) Prevalence of fetal alcohol spectrum disorders in 4 US communities. *JAMA* 319:474–482. <https://doi.org/10.1001/jama.2017.21896>
- Lange S, Probst C, Gmel G, Rehm J, Popova S (2017) Global prevalence of fetal alcohol spectrum disorder among children and youth: a systematic review and meta-analysis. *JAMA Ped*. <https://doi.org/10.1001/jamapediatrics.2017.1919>
- Abel EL, Hannigan JH (1995) Maternal risk factors in fetal alcohol syndrome: provocative and permissive influences. *Neurotoxicol Teratol* 17:445–462. [https://doi.org/10.1016/0892-0362\(95\)98055-6](https://doi.org/10.1016/0892-0362(95)98055-6)
- Popova S, Lange S, Probst C, Gmel G, Rehm J (2017) Estimation of national, regional, and global prevalence of alcohol use during pregnancy and fetal alcohol syndrome: a systematic review and meta-analysis. *Lancet Glob Health* 5:e290–e299. [https://doi.org/10.1016/S2214-109X\(17\)30021-9](https://doi.org/10.1016/S2214-109X(17)30021-9)
- Schneider ML, Moore CF, Adkins MM (2011) The effects of prenatal alcohol exposure on behavior: rodent and primate studies. *Neuropsychol Rev* 21:186–203
- Gray R (2014) Fetal alcohol syndrome: the causal web from disadvantage to birth defect. In: Carpenter B, Blackburn C, Egerton J (eds) *Fetal alcohol spectrum disorders: interdisciplinary perspectives*. Routledge, Oxon, pp 27–38
- Gordis L (2014) *Epidemiology*. Elsevier, Philadelphia
- Daniel R (2015) An introduction to causal inference: counterfactuals and causal diagrams. Paper presented at: Advanced Course in Epidemiological Analysis, London School of Hygiene and Tropical Medicine
- Kramer M (2015) Uses and misuses of causal language. *BJOG* 122:462–463
- Davey Smith G (2008) Assessing intrauterine influences on offspring health outcomes: can epidemiological studies yield robust findings? *Basic Clin Pharmacol Toxicol* 102:245–256
- Tennant PWG, Arnold K, Berrie L, Ellison G, Gilthorpe MS (2017) Advanced modelling strategies: challenges and pitfalls in robust causal inference with observational data. University of Leeds, Leeds
- Pearl J (2009) *Causality: models, reasoning and inference*, 2nd edn. Cambridge University Press, New York
- Glymour MM, Greenland S (2008) Causal Diagrams. In: Rothman KJ, Greenland S, Lash TL (eds) *Modern Epidemiology*. Lippincott Williams & Wilkins, Philadelphia, pp 183–209
- Bandoli G, Coles CD, Kable JA, Wertelecki W, Granovska IV, Pashtepa AO et al (2016) Assessing the independent and joint effects of unmedicated prenatal depressive symptoms and alcohol consumption in pregnancy and infant neurodevelopmental outcomes. *Alcohol Clin Exp Res* 40:1304–1311. <https://doi.org/10.1111/acer.13081>
- Esper LH, Furtado EF (2014) Identifying maternal risk factors associated with fetal alcohol spectrum disorders: a systematic review. *Eur Child Adolesc Psychiatry* 23:877–889. <https://doi.org/10.1007/s00787-014-0603-2>
- Bolling K, Grant C, Hamlyn B, Thornton A (2007) *Infant Feeding Survey 2005: a survey conducted on behalf of the Information Centre for Health and Social Care and the UK Health Departments*. Health and Social Care Information Centre, London
- McAndrew F, Thompson J, Fellows L, Large A, Speed M, Renfrew MJ (2012) *Infant Feeding Survey 2010: a survey carried out on behalf of Health and Social Care Information Centre by IFF Research in partnership with Professor Mary Renfrew, Professor of Mother and Infant Health, College of Medicine, Dentistry and Nursing, University of Dundee*. Health and Social Care Information Centre, London
- Office of Population Censuses and Surveys (1993) *Infant feeding survey, 1990*. UK Data Service, Essex
- Connelly R, Platt L (2014) Cohort profile: UK Millennium Cohort Study (MCS). *Int J Epidemiol* 43:1719–1725
- Fraser A, Macdonald-Wallis C, Tilling K et al (2013) Cohort profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *Int J Epidemiol* 42:97–110
- University of British Columbia (2017) *Fetal alcohol spectrum disorders: results and relevance. Integrating research, policy and promising practice across the world. 7th international conference on FASD, Vancouver, BC*
- University of British Columbia (2015): *results and relevance. Integrating research, policy, and promising practice around the world. 6th international conference on FASD, Vancouver, BC*
- European FASD Alliance (EUFASD) *European conference on FASD (2016)*. Royal Holloway, University of London, Surrey
- Lawlor DA, Tilling K, Smith GD (2016) Triangulation in aetiological epidemiology. *Int J Epidemiol* 45:1866–1886
- Textor J, Hardt J, Knüppel S (2011) DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology* 22:745. <https://doi.org/10.1097/EDE.0b013e318225c2be>
- Burd L, Roberts D, Olson M, Odendaal H (2007) Ethanol and the placenta: a review. *J Matern Fetal Neonatal Med* 20:361–375
- May PA, Blankenship J, Marais A-S et al (2013) Maternal alcohol consumption producing fetal alcohol spectrum disorders (FASD): quantity, frequency, and timing of drinking. *Drug Alcohol Depend* 133:502–512
- Cannon MJ, Dominique Y, O’Leary LA, Snizek JE, Floyd RL, Team FA (2012) Characteristics and behaviors of mothers who have a child with fetal alcohol syndrome. *Neurotoxicol Teratol* 34:90–95
- Coyne KL, De Costa CM, Heazlewood RJ, Newman HC (2008) Pregnancy characteristics of women giving birth to children with fetal alcohol syndrome in Far North Queensland. *Aust N Z J Obstet Gynaecol* 48:240–247. <https://doi.org/10.1111/j.1479-828X.2008.00861.x>

32. Kvigne VL, Leonardson GR, Borzelleca J, Brock E, Neff-Smith M, Welty TK (2003) Characteristics of mothers who have children with fetal alcohol syndrome or some characteristics of fetal alcohol syndrome. *J Am Board Fam Pract* 16:296–303
33. May PA, Gossage JP, Marais A-S et al (2008) Maternal risk factors for fetal alcohol syndrome and partial fetal alcohol syndrome in South Africa: a third study. *Alcohol Clin Exp Res* 32:738–753. <https://doi.org/10.1111/j.1530-0277.2008.00634.x>
34. May PA, Baete A, Russo J et al (2014) Prevalence and characteristics of fetal alcohol spectrum disorders. *Pediatrics* 134:855–866. <https://doi.org/10.1542/peds.2013-3319>
35. Henderson J, Gray R, Brocklehurst P (2007) Systematic review of effects of low–moderate prenatal alcohol exposure on pregnancy outcome. *BJOG* 114:243–252. <https://doi.org/10.1111/j.1471-0528.2006.01163.x>
36. O’Leary CM, Bower C (2012) Guidelines for pregnancy: what’s an acceptable risk, and how is the evidence (finally) shaping up? *Drug Alcohol Rev* 31:170–183
37. Scholder S, Wehby GL, Lewis S, Zuccolo L (2014) Alcohol exposure in utero and child academic achievement. *Econ J* 124:634–667. <https://doi.org/10.1111/econj.12144>
38. Lewis SJ, Zuccolo L, Smith GD et al (2012) Fetal alcohol exposure and IQ at age 8: evidence from a population-based birth-cohort study. *PLoS One* 7:e49407. <https://doi.org/10.1371/journal.pone.0049407>
39. Gray R (2013) Low-to-moderate alcohol consumption during pregnancy and child development—moving beyond observational studies. *BJOG* 120:1039–1041. <https://doi.org/10.1111/1471-0528.12211>
40. Kelly Y, Sacker A, Gray R, Kelly J, Wolke D, Quigley MA (2009) Light drinking in pregnancy, a risk for behavioural problems and cognitive deficits at 3 years of age? *Int J Epidemiol* 38:129–140. <https://doi.org/10.1093/ije/dyn230>
41. Alati R, Macleod J, Hickman M et al (2008) Intrauterine exposure to alcohol and tobacco use and childhood IQ: findings from a parental-offspring comparison within the avon longitudinal study of parents and children. *Pediatr Res* 64:659–666
42. Zuccolo L, DeRoo LA, Wills AK et al (2016) Pre-conception and prenatal alcohol exposure from mothers and fathers drinking and head circumference: results from the Norwegian Mother–Child Study (MoBa). *Sci Rep* 7:39535. <https://doi.org/10.1038/srep39535>
43. Murray J, Burgess S, Zuccolo L, Hickman M, Gray R, Lewis SJ (2016) Moderate alcohol drinking in pregnancy increases risk for children’s persistent conduct problems: causal effects in a Mendelian randomisation study. *J Child Psychol Psychiatry* 57:575–584. <https://doi.org/10.1111/jcpp.12486>
44. Mamluk L, Edwards HB, Savović J et al (2017) Low alcohol consumption and pregnancy and childhood outcomes: time to change guidelines indicating apparently ‘safe’ levels of alcohol during pregnancy? A systematic review and meta-analyses. *BMJ Open* 7:e015410. <https://doi.org/10.1136/bmjopen-2016-015410>
45. Frezza M, di Padova C, Pozzato G, Terpin M, Baraona E, Lieber CS (1990) High blood alcohol levels in women: the role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. *N Engl J Med* 322:95–99
46. Fawehinmi TO, Ilomaki J, Voutilainen S, Kauhanen J (2012) Alcohol consumption and dietary patterns: the FinDrink study. *PLoS One* 7:e38607
47. Manari AP, Preedy VR, Peters TJ (2003) Nutritional intake of hazardous drinkers and dependent alcoholics in the UK. *Addiction Biol* 8:201–210
48. Wilkens Knudsen A, Jensen JE, Nordgaard-Lassen I, Almdal T, Kondrup J, Becker U (2014) Nutritional intake and status in persons with alcohol dependency: data from an outpatient treatment programme. *Eur J Nutr* 53:1483–1492
49. Weinberg J (1984) Nutritional issues in perinatal alcohol exposure. *Neurobehav Toxicol Teratol* 6:261–269
50. Public Health Wales Observatory (2014) Alcohol and health in Wales 2014: Wales profile. Public Health Wales/NHS Trust, Cardiff. <http://www.wales.nhs.uk/sitesplus/922/page/75229>. Accessed 17 Oct 2014
51. Health and Social Care Information Centre (HSCIC) (2013) Health Survey for England—2012. <https://digital.nhs.uk/catalogue/PUB13218>. Accessed 2 Mar 2018
52. Inskip HM, Crozier SR, Godfrey KM, Borland SE, Cooper C, Robinson SM (2009) Women’s compliance with nutrition and lifestyle recommendations before pregnancy: general population cohort study. *BMJ* 338:b481
53. Naimi TS, Lipscomb LE, Brewer RD, Gilbert BC (2003) Binge drinking in the preconception period and the risk of unintended pregnancy: implications for women and their children. *Pediatrics* 111:1136–1141
54. Oulman E, Kim THM, Yunis K, Tamim H (2015) Prevalence and predictors of unintended pregnancy among women: an analysis of the Canadian Maternity Experiences Survey. *BMC Pregnancy Childbirth* 15:1–8. <https://doi.org/10.1186/s12884-015-0663-4>
55. Ethen MK, Ramadhani TA, Scheuerle AE et al (2009) Alcohol consumption by women before and during pregnancy. *Matern Child Health J* 13:274–285. <https://doi.org/10.1007/s10995-008-0328-2>
56. Wellings K, Jones KG, Mercer CH et al (2013) The prevalence of unplanned pregnancy and associated factors in Britain: findings from the third National Survey of Sexual Attitudes and Lifestyles (Natsal-3). *Lancet* 382:1807–1816. [https://doi.org/10.1016/S0140-6736\(13\)62071-1](https://doi.org/10.1016/S0140-6736(13)62071-1)
57. May PA, Brooke L, Gossage JP et al (2000) Epidemiology of Fetal Alcohol Syndrome in a South African Community in the Western Cape Province. *Am J Public Health* 90:1905–1912
58. May PA, de Vries MM, Marais A-S et al (2016) The continuum of fetal alcohol spectrum disorders in four rural communities in South Africa: prevalence and characteristics. *Drug Alcohol Depend* 159:207–218. <https://doi.org/10.1016/j.drugalcdep.2015.12.023>
59. May PA, Gossage JP, Brooke LE et al (2005) Maternal risk factors for fetal alcohol syndrome in the Western cape province of South Africa: a population-based study. *Am J Public Health* 95:1190–1199
60. May PA, Tabachnick BG, Gossage JP et al (2011) Maternal risk factors predicting child physical characteristics and dysmorphology in fetal alcohol syndrome and partial fetal alcohol syndrome. *Drug Alcohol Depend* 119:18–27
61. Urban MF, Chersich MF, Fourie L-A, Chetty C, Olivier L, Viljoen D (2008) Fetal alcohol syndrome among grade-one children in the Northern Cape Province: prevalence and risk factors. *S Afr Med J* 98:877–882
62. Viljoen D, Croxford J, Gossage JP, Kodituwakku PW, May PA (2002) Characteristics of mothers of children with fetal alcohol syndrome in the Western Cape Province of South Africa: a case control study. *J Stud Alcohol* 63:6–17
63. Ceccanti M, Fiorentino D, Coriale G et al (2014) Maternal risk factors for fetal alcohol spectrum disorders in a province in Italy. *Drug Alcohol Depend* 145:201–208. <https://doi.org/10.1016/j.drugalcdep.2014.10.017>
64. May PA, Fiorentino D, Coriale G et al (2011) Prevalence of children with severe fetal alcohol spectrum disorders in communities near Rome, Italy: new estimated rates are higher than previous estimates. *Int J Environ Res Public Health* 8:2331–2351
65. May PA, Fiorentino D, Gossage J et al (2006) Epidemiology of FASD in a province in Italy: prevalence and characteristics of

- children in a random sample of schools. *Alcohol Clin Exp Res* 30:1562–1575
66. Odendaal HJ, Steyn DW, Elliott A, Burd L (2009) Combined effects of cigarette smoking and alcohol consumption on perinatal outcome. *Gynecol Obstet Invest* 67:1–8
 67. Heller M, Burd L (2014) Review of ethanol dispersion, distribution, and elimination from the fetal compartment. *Birth Defects Res A Clin Mol Teratol* 100:277–283
 68. Janisse JJ, Bailey BA, Ager J, Sokol RJ (2014) Alcohol, tobacco, cocaine, and marijuana use: relative contributions to preterm delivery and fetal growth restriction. *Subst Abus* 35:60–67. <https://doi.org/10.1080/08897077.2013.804483>
 69. Julvez J, Ribas-Fitó N, Torrent M, Fornes M, Garcia-Esteban R, Sunyer J (2007) Maternal smoking habits and cognitive development of children at age 4 years in a population-based birth cohort. *Int J Epidemiol* 36:825–832
 70. Ko T-J, Tsai L-Y, Chu L-C et al (2014) Parental smoking during pregnancy and its association with low birth weight, small for gestational age, and preterm birth offspring: a birth cohort study. *Pediatr Neonatol* 55:20–27. <https://doi.org/10.1016/j.pedneo.2013.05.005>
 71. Bada HS, Das A, Bauer CR et al (2005) Low birth weight and preterm births: etiologic fraction attributable to prenatal drug exposure. *J Perinatol* 25:631–637
 72. Chiriboga CA (2003) Fetal alcohol and drug effects. *Neurologist* 9:267–279
 73. Murphy DJ, Dunney C, Mullally A, Adnan N, Deane R (2013) Population-based study of smoking behaviour throughout pregnancy and adverse perinatal outcomes. *Int J Environ Res Public Health* 10:3855–3867. <https://doi.org/10.3390/ijerph10093855>
 74. Tiesler CMT, Heinrich J (2014) Prenatal nicotine exposure and child behavioural problems. *Eur Child Adolesc Psychiatry* 23:913–929. <https://doi.org/10.1007/s00787-014-0615-y>
 75. Piper BJ, Corbett SM (2012) Executive function profile in the offspring of women that smoked during pregnancy. *Nicotine Tob Res* 14:191–199
 76. Abel EL, Hannigan JH (1995) ‘J-shaped’ relationship between drinking during pregnancy and birth weight: reanalysis of prospective epidemiological data. *Alcohol Alcohol* 30:345–355
 77. Lange S, Probst C, Quere M, Rehm J, Popova S (2015) Alcohol use, smoking and their co-occurrence during pregnancy among Canadian women, 2003 to 2011/12. *Addict Behav* 50:102–109. <https://doi.org/10.1016/j.addbeh.2015.06.018>
 78. May PA, Keaster C, Bozeman R et al (2015) Prevalence and characteristics of fetal alcohol syndrome and partial fetal alcohol syndrome in a Rocky Mountain Region City. *Drug Alcohol Depend* 155:118–127
 79. Keegan J, Parva M, Finnegan M, Gerson A, Belden M (2010) Addiction in pregnancy. *J Addict Dis* 29:175–191
 80. Wendell AD (2013) Overview and epidemiology of substance abuse in pregnancy. *Clin Obstet Gynecol* 56:91–96
 81. Davies JK, Bledsoe JM (2005) Prenatal alcohol and drug exposures in adoption. *Pediatr Clin North Am* 52:1369–1393
 82. Lumeng JC, Cabral HJ, Gannon K, Heeren T, Frank DA (2007) Pre-natal exposures to cocaine and alcohol and physical growth patterns to age 8 years. *Neurotoxicol Teratol* 29:446–457
 83. Schempf AH, Strobino DM (2008) Illicit drug use and adverse birth outcomes: is it drugs or context? *J Urban Health* 85:858–873. <https://doi.org/10.1007/s11524-008-9315-6>
 84. Bailey BA, McCook JG, Hodge A, McGrady L (2012) Infant birth outcomes among substance using women: why quitting smoking during pregnancy is just as important as quitting illicit drug use. *Matern Child Health J* 16:414–422. <https://doi.org/10.1007/s10995-011-0776-y>
 85. Fried PA, Watkinson B, Gray R (1998) Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marihuana. *Neurotoxicol Teratol* 20:293–306. [https://doi.org/10.1016/S0892-0362\(97\)00091-3](https://doi.org/10.1016/S0892-0362(97)00091-3)
 86. Fried PA, Watkinson B, Gray R (2003) Differential effects on cognitive functioning in 13- to 16-year-olds prenatally exposed to cigarettes and marihuana. *Neurotoxicol Teratol* 25:427–436. [https://doi.org/10.1016/S0892-0362\(03\)00029-1](https://doi.org/10.1016/S0892-0362(03)00029-1)
 87. Faden VB, Graubard BI (2000) Maternal substance use during pregnancy and developmental outcome at age three. *J Subst Abuse* 12:329–340
 88. Fish EW, Gilbert MT, Murdaugh LB, Williams KP, Sulik KK, Parnell SE (2016) Synergistic actions of ethanol and synthetic cannabinoids during early gestation in a mouse model: teratogenesis and potential mechanisms. Paper presented at the EUFASD 2016, Royal Holloway, University of London, Surrey
 89. Cone-Wesson B (2005) Prenatal alcohol and cocaine exposure: influences on cognition, speech, language, and hearing. *J Commun Disord* 38:279–302
 90. D’Apolito K (1998) Substance abuse: infant and childhood outcomes. *J Pediatr Nurs* 13:307–316
 91. Beeghly M, Rose-Jacobs R, Martin BM, Cabral HJ, Heeren TC, Frank DA (2014) Level of intrauterine cocaine exposure and neuropsychological test scores in preadolescence: subtle effects on auditory attention and narrative memory. *Neurotoxicol Teratol* 45:1–17
 92. Chang L, Smith LM, LoPresti C, Yonekura ML, Kuo J, Walot I, Ernst T (2004) Smaller subcortical volumes and cognitive deficits in children with prenatal methamphetamine exposure. *Psychiatry Res* 132:95–106. <https://doi.org/10.1016/j.psycyhres.2004.06.004>
 93. Billing L, Eriksson M, Jonsson B, Steneroth G, Zetterström R (1994) The influence of environmental factors on behavioural problems in 8-year-old children exposed to amphetamine during fetal life. *Child Abuse Negl* 18:3–9. [https://doi.org/10.1016/0145-2134\(94\)90091-4](https://doi.org/10.1016/0145-2134(94)90091-4)
 94. Eriksson M, Billing L, Steneroth G, Zetterstrom R (1989) Health and development of 8-year-old children whose mothers abused amphetamine during pregnancy. *Acta Paediatr* 78:944–949. <https://doi.org/10.1111/j.1651-2227.1989.tb11179.x>
 95. Kuczkowski KM (2007) The effects of drug abuse on pregnancy. *Curr Opin Obstet Gynecol* 19:578–585
 96. Dube SR, Felitti VJ, Dong M, Chapman DP, Giles WH, Anda RF (2003) Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use: the adverse childhood experiences study. *Pediatrics* 111:564–572. <https://doi.org/10.1542/peds.111.3.564>
 97. National Institute for Health and Care Excellence (NICE) (2010) Pregnancy and complex social factors: a model for service provision for pregnant women with complex social factors. NICE Clinical Guideline [CG110]. NICE, London
 98. Young JK, Giesbrecht HE, Eskin MN, Aliani M, Suh M (2014) Nutrition implications for fetal alcohol spectrum disorders. *Adv Nutr* 5:675–692
 99. May PA, Gossage JP (2011) Maternal risk factors for fetal alcohol spectrum disorders: not as simple as it might seem. *Alcohol Res Health* 34:15–26
 100. Barker ED, Kirkham N, Ng J, Jensen SKG (2013) Prenatal maternal depression symptoms and nutrition, and child cognitive function. *Br J Psychiatry* 203:417–421. <https://doi.org/10.1192/bjp.bp.113.129486>
 101. Pina-Camacho L, Jensen S, Gaysina D, Barker E (2015) Maternal depression symptoms, unhealthy diet and child emotional-behavioural dysregulation. *Psychol Med* 45:1851–1860
 102. Coathup V, Northstone K, Gray R, Wheeler S, Smith L (2017) Dietary patterns and alcohol consumption during pregnancy: secondary analysis of Avon Longitudinal Study of Parents and

- Children. *Alcohol Clin Exp Res* 41:1120–1128. <https://doi.org/10.1111/acer.13379>
103. Otero NK, Thomas JD, Saski CA, Xia X, Kelly SJ (2012) Choline supplementation and DNA methylation in the hippocampus and prefrontal cortex of rats exposed to alcohol during development. *Alcohol Clin Exp Res* 36:1701–1709. <https://doi.org/10.1111/j.1530-0277.2012.01784.x>
 104. Shankar K, Hildestrand M, Liu X et al (2006) Physiologic and genomic analyses of nutrition-ethanol interactions during gestation: implications for fetal ethanol toxicity. *Exp Biol Med* 231:1379–1397
 105. Keen CL, Uriu-Adams JY, Skalny A et al (2010) The plausibility of maternal nutritional status being a contributing factor to the risk for fetal alcohol spectrum disorders: the potential influence of zinc status as an example. *BioFactors* 36:125–135. <https://doi.org/10.1002/biof.89>
 106. Idrus NM, Breit KR, Thomas JD (2017) Dietary choline levels modify the effects of prenatal alcohol exposure in rats. *Neurotoxicol Teratol* 59:43–52. <https://doi.org/10.1016/j.ntt.2016.11.007>
 107. May PA, Hamrick KJ, Corbin KD et al (2014) Dietary intake, nutrition, and fetal alcohol spectrum disorders in the Western Cape Province of South Africa. *Reprod Toxicol* 46:31–39. <https://doi.org/10.1016/j.reprotox.2014.02.002>
 108. Hannigan JH, Abel EL, Kruger ML (1993) “Population” characteristics of birthweight in an animal model of alcohol-related developmental effects. *Neurotoxicol Teratol* 15:97–105. [https://doi.org/10.1016/0892-0362\(93\)90068-Y](https://doi.org/10.1016/0892-0362(93)90068-Y)
 109. Deltour L, Ang HL, Duester G (1996) Ethanol inhibition of retinoic acid synthesis as a potential mechanism for fetal alcohol syndrome. *FASEB J* 10:1050–1057
 110. Duester G (1991) A hypothetical mechanism for fetal alcohol syndrome involving ethanol inhibition of retinoic acid synthesis at the alcohol dehydrogenase step. *Alcohol Clin Exp Res* 15:568–572
 111. Fisher SE, Karl PI (1988) Maternal ethanol use and selective fetal malnutrition. *Recent Dev Alcohol* 6:277–289
 112. Henderson GI, Patwardhan RV, McLeroy S, Schenker S (1982) Inhibition of placental amino acid uptake in rats following acute and chronic ethanol exposure. *Alcohol Clin Exp Res* 6:495–505. <https://doi.org/10.1111/j.1530-0277.1982.tb05013.x>
 113. Coles CD, Kable JA, Keen CL et al (2015) Dose and timing of prenatal alcohol exposure and maternal nutritional supplements: developmental effects on 6-month-old infants. *Matern Child Health J* 19:2605–2614. <https://doi.org/10.1007/s10995-015-1779-x>
 114. Kable JA, Coles CD, Keen CL et al (2015) The impact of micronutrient supplementation in alcohol-exposed pregnancies on information processing skills in Ukrainian infants. *Alcohol* 49:647–656. <https://doi.org/10.1016/j.alcohol.2015.08.005>
 115. Nguyen TT, Risbud RD, Mattson SN, Chambers CD, Thomas JD (2016) Randomized, double-blind, placebo-controlled clinical trial of choline supplementation in school-aged children with fetal alcohol spectrum disorders. *Am J Clin Nutr* 104:1683–1692. <https://doi.org/10.3945/ajcn.116.142075>
 116. Foster K, Lader D, Cheesbrough S (1997) Infant Feeding 1995: results from a survey carried out by the Social Survey Division of ONS on behalf of the UK health departments. The Stationery Office Ltd., London
 117. Hamlyn B, Brooker S, Oleinikova K, Wands S (2002) Infant Feeding 2000: a survey conducted on behalf of the Department of Health, the Scottish Executive, the National Assembly for Wales and the Department of Health, Social Services and Public Safety in Northern Ireland. The Stationery Office Ltd., London
 118. Nykjaer C, Alwan NA, Greenwood DC et al (2014) Maternal alcohol intake prior to and during pregnancy and risk of adverse birth outcomes: evidence from a British cohort. *J Epidemiol Commun Health* 68:542–549. <https://doi.org/10.1136/jech-2013-202934>
 119. Mårdby A-C, Lupattelli A, Hensing G, Nordeng H (2017) Consumption of alcohol during pregnancy: a multinational European study. *Women Birth* 30:e207–e213. <https://doi.org/10.1016/j.wombi.2017.01.003>
 120. Church MW, Abel EL, Dintcheff BA, Matyjasik C (1990) Maternal age and blood alcohol concentration in the pregnant Long-Evans rat. *J Pharmacol Exp Ther* 253:192–199
 121. Kim YC, Kim SY, Sohn YR (2003) Effect of age increase on metabolism and toxicity of ethanol in female rats. *Life Sci* 74:509–519
 122. Vestal RE, McGuire EA, Tobin JD, Andres R, Norris AH, Mezey E (1977) Aging and ethanol metabolism. *Clin Pharmacol Ther* 21:343–354
 123. Vogel-Sprott M, Barrett P (1984) Age, drinking habits and the effects of alcohol. *J Stud Alcohol* 45:517–521. <https://doi.org/10.15288/jsa.1984.45.517>
 124. Jacobson SW, Jacobson JL, Sokol RJ, Chiodo LM, Corobana R (2004) Maternal age, alcohol abuse history, and quality of parenting as moderators of the effects of prenatal alcohol exposure on 7.5-year intellectual function. *Alcohol Clin Exp Res* 28:1732–1745. <https://doi.org/10.1097/01.ALC.0000145691.81233.FA>
 125. Fernandez V, Kriz A, Videla LA (1988) Age-dependent changes in in vivo ethanol metabolism and in the activity of hepatic enzymes involved in ethanol oxidation and microsomal functions. *Cell Biochem Funct* 6:7–12
 126. Hahn HK, Burch RE (1983) Impaired ethanol metabolism with advancing age. *Alcohol Clin Exp Res* 7:299–301
 127. Pozzato G, Moretti M, Franzin F et al (1995) Ethanol metabolism and aging: the role of “first pass metabolism” and gastric alcohol dehydrogenase activity. *J Gerontol A Biol Sci Med Sci* 50:B135–B141
 128. Rikans LE, Snowden CD, Moore DR (1990) Influence of aging on ethanol and acetaldehyde oxidation in female rat liver. *Gerontology* 36:185–192
 129. Seitz HK, Meydani M, Ferschke I, Simanowski UA, Boesche J, Bogusz M, Hoepker WW, Blumberg JB, Russell RM (1989) Effect of aging on in vivo and in vitro ethanol metabolism and its toxicity in F344 rats. *Gastroenterology* 97:446–456
 130. Seitz HK, Xu Y, Simanowski UA, Osswald B (1992) Effect of age and gender on in vivo ethanol elimination, hepatic alcohol dehydrogenase activity, and NAD⁺ availability in F344 rats. *Res Exp Med* 192:205–212
 131. Fisher SE, Atkinson M, Burnap JK, Jacobson S, Sehgal PK, Scott W, Van Thiel DH (1982) Ethanol-associated selective fetal malnutrition: a contributing factor in the fetal alcohol syndrome. *Alcohol Clin Exp Res* 6:197–201
 132. May PA, Gossage JP, White-Country M, Goodhart K, Decoteau S, Trujillo PM, Kalberg WO, Viljoen DL, Hoyme HE (2004) Alcohol consumption and other maternal risk factors for fetal alcohol syndrome among three distinct samples of women before, during, and after pregnancy: the risk is relative. *Am J Med Genet C Semin Med Genet* 127C:10–20. <https://doi.org/10.1002/ajmg.c.30011>
 133. Michalak L, Trocki K, Bond J (2007) Religion and alcohol in the US National Alcohol Survey: how important is religion for abstinence and drinking? *Drug Alcohol Depend* 87:268–280. <https://doi.org/10.1016/j.drugalcdep.2006.07.013>
 134. Astley SJ, Bailey D, Talbot C, Clarren SK (2000) Fetal alcohol syndrome (FAS) primary prevention through FAS diagnosis: II. A comprehensive profile of 80 birth mothers of children with FAS. *Alcohol Alcohol* 35:509–519

135. Finer LB, Zolna MR (2011) Unintended pregnancy in the United States: incidence and disparities, 2006. *Contraception* 84:478–485. <https://doi.org/10.1016/j.contraception.2011.07.013>
136. Abel EL, Dintcheff BA (1984) Factors affecting the outcome of maternal alcohol exposure: I. Parity. *Neurobehav Toxicol Teratol* 6:373–377
137. Abel EL, Dintcheff BA (1985) Factors affecting the outcome of maternal alcohol exposure: II. Maternal age. *Neurobehav Toxicol Teratol* 7:263–266
138. Bagheri MM, Burd L, Martsolf JT, Klug MG (1998) Fetal alcohol syndrome: maternal and neonatal characteristics. *J Perinat Med* 26:263–269. <https://doi.org/10.1515/jpme.1998.26.4.263>
139. Miller LA, Shaikh T, Stanton C, Montgomery A, Rickard R, Sharon K, Hoffman R (1995) Surveillance for fetal alcohol syndrome in Colorado. *Public Health Rep* 110:690–697. <https://doi.org/10.2307/4597935>
140. Costa DD, Dritsa M, Larouche J, Brender W (2000) Psychosocial predictors of labor/delivery complications and infant birth weight: a prospective multivariate study. *J Psychosom Obstet Gynaecol* 21:137–148. <https://doi.org/10.3109/01674820009075621>
141. Johnson RC, Slade P (2003) Obstetric complications and anxiety during pregnancy: is there a relationship? *J Psychosom Obstet Gynaecol* 24:1–14. <https://doi.org/10.3109/01674820309042796>
142. Cnattingius S (2004) The epidemiology of smoking during pregnancy: smoking prevalence, maternal characteristics, and pregnancy outcomes. *Nicotine Tob Res* 6:S125–S140. <https://doi.org/10.1080/14622200410001669187>
143. Drug and Therapeutics Bulletin (2016) Vitamin supplementation in pregnancy. *Drug Ther Bull* 54:81–84. <https://doi.org/10.1136/dtb.2016.7.0414>
144. National Institute for Health and Care Excellence (NICE) (2008) Antenatal care for uncomplicated pregnancies. NICE Clinical Guideline 62. NICE, London
145. Public Health Wales/NHS Wales (2014) Bump, baby and beyond. Public Health Wales/NHS Trust, Cardiff
146. Brown QL, Hasin DS, Keyes KM, Fink DS, Ravenell O, Martins SS (2016) Health insurance, alcohol and tobacco use among pregnant and non-pregnant women of reproductive age. *Drug Alcohol Depend* 166:116–124. <https://doi.org/10.1016/j.drugalcdep.2016.07.001>
147. Sedgh G, Singh S, Hussain R (2014) Intended and unintended pregnancies worldwide in 2012 and recent trends. *Stud Fam Plan* 45:301–314. <https://doi.org/10.1111/j.1728-4465.2014.00393.x>
148. Ingersoll KS, Ceperich SD, Nettleman MD, Johnson BA (2008) Risk drinking and contraception effectiveness among college women. *Psychol Health* 23:965–981
149. O’Keeffe LM, Dahly DL, Murphy M et al (2016) Positive lifestyle changes around the time of pregnancy: a cross-sectional study. *BMJ Open* 6:e010233. <https://doi.org/10.1136/bmjopen-2015-010233>
150. Dott M, Rasmussen SA, Hogue CJ, Reefhuis J (2010) Association between pregnancy intention and reproductive-health related behaviors before and after pregnancy recognition, national birth defects prevention study, 1997–2002. *Matern Child Health J* 14:373–381. <https://doi.org/10.1007/s10995-009-0458-1>
151. Watt MH, Eaton LA, Choi KW, Velloza J, Kalichman SC, Skinner D, Sikkema KJ (2014) “It’s better for me to drink, at least the stress is going away”: perspectives on alcohol use during pregnancy among South African women attending drinking establishments. *Soc Sci Med* 116:119–125. <https://doi.org/10.1016/j.socscimed.2014.06.048>
152. Rahman M, Sasagawa T, Fujii R, Tomizawa H, Makinoda S (2012) Intimate partner violence and unintended pregnancy among Bangladeshi women. *J Interpers Violence* 27:2999–3015. <https://doi.org/10.1177/0886260512441072>
153. Miller E, Decker MR, McCauley HL, Tancredi DJ, Levenson RR, Waldman J (2010) Pregnancy coercion, intimate partner violence and unintended pregnancy. *Contraception* 81:316–322. <https://doi.org/10.1016/j.contraception.2009.12.004>
154. Castelo-Branco C, Parera N, Mendoza N, Pérez-Campos E, Lete I (2014) Alcohol and drug abuse and risky sexual behaviours in young adult women. *Gynecol Endocrinol* 30:581–586
155. Sharpe TT, Velasquez MM (2008) Risk of alcohol-exposed pregnancies among low-income, illicit drug-using women. *J Womens Health* 17:1339–1344
156. Carmichael SL, Shaw GM (2000) Maternal life event stress and congenital anomalies. *Epidemiology* 11:30–35
157. Schneider ML, Roughton EC, Lubach GR (1997) Moderate alcohol consumption and psychological stress during pregnancy induce attention and neuromotor impairments in primate infants. *Child Dev* 68:747–759
158. Schneider ML, Moore CF, Kraemer GW (2001) Moderate alcohol during pregnancy: learning and behavior in adolescent rhesus monkeys. *Alcohol Clin Exp Res* 25:1383–1392. <https://doi.org/10.1111/j.1530-0277.2001.tb02362.x>
159. Schneider ML, Moore CF, Kraemer GW, Roberts AD, DeJesus OT (2002) The impact of prenatal stress, fetal alcohol exposure, or both on development: perspectives from a primate model. *Psychoneuroendocrinology* 27:285–298
160. Staples MC, Porch MW, Savage DD (2014) Impact of combined prenatal ethanol and prenatal stress exposures on markers of activity-dependent synaptic plasticity in rat dentate gyrus. *Alcohol* 48:523–532
161. Staples MC, Rosenberg MJ, Allen NA, Porch MW, Savage DD (2013) Impact of combined prenatal ethanol and prenatal stress exposure on anxiety and hippocampal-sensitive learning in adult offspring. *Alcohol Clin Exp Res* 37:2039–2047
162. Schneider ML, Moore CF, Kraemer GW (2004) Moderate level alcohol during pregnancy, prenatal stress, or both and limbic-hypothalamic-pituitary-adrenocortical axis response to stress in rhesus monkeys. *Child Dev* 75:96–109
163. Weinberg J, Sliwowska JH, Lan N, Hellemans KGC (2008) Prenatal alcohol exposure: foetal programming, the hypothalamic-pituitary-adrenal axis and sex differences in outcome. *J Neuroendocrinol* 20:470–488. <https://doi.org/10.1111/j.1365-2826.2008.01669.x>
164. Hennekens CH, Buring JE, Mayrent SL (1987) *Epidemiology in medicine*. Little Brown and Company, Boston
165. Beijers R, Buitelaar JK, de Weerth C (2014) Mechanisms underlying the effects of prenatal psychosocial stress on child outcomes: beyond the HPA axis. *Eur Child Adolesc Psychiatry* 23:943–956. <https://doi.org/10.1007/s00787-014-0566-3>
166. Carmichael SL, Shaw GM, Yang W, Abrams B, Lammer EJ (2007) Maternal stressful life events and risks of birth defects. *Epidemiology* 18:356–361. <https://doi.org/10.1097/01.ede.0000259986.85239.87>
167. Suarez L, Cardarelli K, Hendricks K (2003) Maternal stress, social support, and risk of neural tube defects among Mexican Americans. *Epidemiology* 14:612–616. <https://doi.org/10.1097/01.ede.0000073270.39780.e9>
168. Palmer SR, Evans A, Broughton H, Huddart S, Drayton M, Rankin J, Draper ES, Cameron A, Paranjthy S (2013) The role of maternal stress in early pregnancy in the aetiology of gastro-schisis: an incident case control study. *PLoS One* 8:e80103. <https://doi.org/10.1371/journal.pone.0080103>
169. O’Donnell KJ, Bugge Jensen A, Freeman L, Khalife N, O’Connor TG, Glover V (2012) Maternal prenatal anxiety and downregulation of placental 11beta-HSD2. *Psychoneuroendocrinology* 37:818–826. <https://doi.org/10.1016/j.psyneuen.2011.09.014>
170. Waters CS, Hay DF, Simmonds JR, van Goozen SH (2014) Antenatal depression and children’s developmental outcomes:

- potential mechanisms and treatment options. *Eur Child Adolesc Psychiatry* 23:957–971. <https://doi.org/10.1007/s00787-014-0582-3>
171. O'Connor TG, Ben-Shlomo Y, Heron J, Golding J, Adams D, Glover V (2005) Prenatal anxiety predicts individual differences in cortisol in pre-adolescent children. *Biol Psychiat* 58:211–217. <https://doi.org/10.1016/j.biopsych.2005.03.032>
 172. Santucci AK, Singer LT, Wisniewski SR, Luther JF, Eng HF, Dills JL, Sit DK, Hanusa BH, Wisner KL (2014) Impact of prenatal exposure to serotonin reuptake inhibitors or maternal major depressive disorder on infant developmental outcomes. *J Clin Psychiatry* 75:1088–1095. <https://doi.org/10.4088/JCP.13m08902>
 173. Bolton JM, Robinson J, Sareen J (2009) Self-medication of mood disorders with alcohol and drugs in the National Epidemiologic Survey on Alcohol and Related Conditions. *J Affect Disord* 115:367–375. <https://doi.org/10.1016/j.jad.2008.10.003>
 174. Briere FN, Rohde P, Seeley JR, Klein D, Lewinsohn PM (2014) Comorbidity between major depression and alcohol use disorder from adolescence to adulthood. *Compr Psychiatry* 55:526–533. <https://doi.org/10.1016/j.comppsy.2013.10.007>
 175. Hanna EZ, Faden VB, Dufour MC (1994) The motivational correlates of drinking, smoking, and illicit drug use during pregnancy. *J Subst Abuse* 6:155–167
 176. Coleman MA, Coleman NC, Murray JP (1990) Mutual support groups to reduce alcohol consumption by pregnant women: marketing implications. *Health Mark Q* 7:47–63
 177. Skagerstrom J, Alehagen S, Haggstrom-Nordin E, Arestedt K, Nilsen P (2013) Prevalence of alcohol use before and during pregnancy and predictors of drinking during pregnancy: a cross sectional study in Sweden. *BMC Public Health* 13:780
 178. Mulia N, Schmidt L, Bond J, Jacobs L, Korcha R (2008) Stress, social support and problem drinking among women in poverty. *Addiction* 103:1283–1293. <https://doi.org/10.1111/j.1360-0443.2008.02234.x>
 179. Frankenberger DJ, Clements-Nolle K, Yang W (2015) The association between adverse childhood experiences and alcohol use during pregnancy in a representative sample of adult women. *Womens Health Issues* 25:688–695
 180. Norberg Å, Jones AW, Hahn RG, Gabrielsson JL (2003) Role of variability in explaining ethanol pharmacokinetics. *Clin Pharmacokinet* 42:1–31
 181. Carter RC, Jacobson JL, Sokol RJ, Avison MJ, Jacobson SW (2013) Fetal alcohol-related growth restriction from birth through young adulthood and moderating effects of maternal prepregnancy weight. *Alcohol Clin Exp Res* 37:452–462
 182. Scott-Pillai R, Spence D, Cardwell CR, Hunter A, Holmes VA (2013) The impact of body mass index on maternal and neonatal outcomes: a retrospective study in a UK obstetric population, 2004–2011. *BJOG* 120:932–939. <https://doi.org/10.1111/1471-0528.12193>
 183. Streissguth A, Barr H, Kogan J, Bookstein F (1996) Understanding the occurrence of secondary disabilities in clients with fetal alcohol syndrome (FAS) and fetal alcohol effects (FAE). Final report to the Centers for Disease Control and Prevention (CDC). CDC, Seattle
 184. Popova S, Lange S, Shield K, Mihic A, Chudley AE, Mukherjee RAS, Bekmuradov D, Rehm J (2016) Comorbidity of fetal alcohol spectrum disorder: a systematic review and meta-analysis. *Lancet* 387:978–987. [https://doi.org/10.1016/S0140-6736\(15\)01345-8](https://doi.org/10.1016/S0140-6736(15)01345-8)
 185. Mukherjee R, Cook PA, Fleming KM, Norgate SH (2016) What can be done to lessen morbidity associated with fetal alcohol spectrum disorders? *Arch Dis Child* 102:463–467. <https://doi.org/10.1136/archdischild-2016-310822>
 186. Mukherjee R, Wray E, Hollins S, Curfs L (2015) What does the general public in the UK know about the risk to a developing foetus if exposed to alcohol in pregnancy? Findings from a UK mixed methodology study. *Child Care Health Dev* 41:467–474. <https://doi.org/10.1111/cch.12187>
 187. Britton A (2016) Alcohol consumption for women trying to conceive. *BMJ* 354:i4540
 188. Mather M, Wiles K, O'Brien P (2015) Should women abstain from alcohol throughout pregnancy? *BMJ* 351:h5232. <https://doi.org/10.1136/bmj.h5232>
 189. Schölin L, Hughes K, Bellis MA, Eriksson C, Porcellato L (2018) Exploring practices and perceptions of alcohol use during pregnancy in England and Sweden through a cross-cultural lens. *Eur J Public Health* 28:533–537. <https://doi.org/10.1093/eurpub/ckx208>
 190. Rhule-Louie DM, McMahon RJ (2007) Problem behavior and romantic relationships: assortative mating, behavior contagion, and desistance. *Clin Child Fam Psychol Rev* 10:53–100. <https://doi.org/10.1007/s10567-006-0016-y>
 191. Nizhnikov ME, Popoola DO, Cameron NM (2016) Transgenerational transmission of the effect of gestational ethanol exposure on ethanol use-related behavior. *Alcohol Clin Exp Res* 40:497–506. <https://doi.org/10.1111/acer.12978>
 192. Edenberg HJ, Foroud T (2006) Review: the genetics of alcoholism: identifying specific genes through family studies. *Addiction Biol* 11:386–396. <https://doi.org/10.1111/j.1369-1600.2006.00035.x>
 193. Bandura A (1986) Social foundations of thought and action: a social cognitive theory. Prentice-Hall Inc., Englewood Cliffs
 194. Ouko LA, Shantikumar K, Knezovich J, Haycock P, Schnugh DJ, Ramsay M (2009) Effect of alcohol consumption on CpG methylation in the differentially methylated regions of H19 and IG-DMR in male gametes—implications for fetal alcohol spectrum disorders. *Alcohol Clin Exp Res* 33:1615–1627. <https://doi.org/10.1111/j.1530-0277.2009.00993.x>
 195. Day J, Savani S, Krempel BD, Nguyen M, Kitlinska JB (2016) Influence of paternal preconception exposures on their offspring: through epigenetics to phenotype. *Am J Stem Cells* 5:11–18
 196. Abel E (2004) Paternal contribution to fetal alcohol syndrome. *Addiction Biol* 9:127–133
 197. Pierog S, Chandavasu O, Wexler I (1979) The fetal alcohol syndrome: some maternal characteristics. *Int J Gynaecol Obstet* 16:412–415
 198. Astley SJ, Bailey D, Talbot C, Clarren SK (2000) Fetal alcohol syndrome (FAS) primary prevention through FAS diagnosis: I. Identification of high-risk birth mothers through the diagnosis of their children. *Alcohol Alcohol* 35:499–508
 199. Green RF, Stoler JM (2007) Alcohol dehydrogenase 1B genotype and fetal alcohol syndrome: a HuGE minireview. *Am J Obstet Gynecol* 197:12–25. <https://doi.org/10.1016/j.ajog.2007.02.028>
 200. Gemma S, Vichi S, Testai E (2007) Metabolic and genetic factors contributing to alcohol induced effects and fetal alcohol syndrome. *Neurosci Biobehav Rev* 31:221–229
 201. Eberhart JK, Parnell SE (2016) The genetics of fetal alcohol spectrum disorders. *Alcohol Clin Exp Res* 40:1154–1165. <https://doi.org/10.1111/acer.13066>
 202. Chasnoff IJ (1985) Fetal alcohol syndrome in twin pregnancy. *Acta Genet Med Gemellol* 34:229–232. <https://doi.org/10.1017/S0001566000004797>
 203. Christoffel KK, Salafsky I (1975) Fetal alcohol syndrome in dizygotic twins. *J Pediatr* 87:963–967. [https://doi.org/10.1016/S0022-3476\(75\)80919-X](https://doi.org/10.1016/S0022-3476(75)80919-X)
 204. Riikonen RS (1994) Difference in susceptibility to teratogenic effects of alcohol in discordant twins exposed to alcohol during the second half of gestation. *Pediatr Neurol* 11:332–336. [https://doi.org/10.1016/0887-8994\(94\)90012-4](https://doi.org/10.1016/0887-8994(94)90012-4)

205. Streissguth AP, Dehaene P (1993) Fetal alcohol syndrome in twins of alcoholic mothers: concordance of diagnosis and IQ. *Am J Med Genet* 47:857–861. <https://doi.org/10.1002/ajmg.1320470612>
206. Becker HC, Diaz-Granados JL, Randall CL (1996) Teratogenic actions of ethanol in the mouse: a minireview. *Pharmacol Biochem Behav* 55:501–513. [https://doi.org/10.1016/S0091-3057\(96\)00255-9](https://doi.org/10.1016/S0091-3057(96)00255-9)
207. Zhou FC, Mason S (eds) (2015) Genetics and epigenetics of fetal alcohol spectrum disorders. Frontiers Media, Lausanne. <https://doi.org/10.3389/978-2-88919-573-2>
208. Viljoen DL, Carr LG, Foroud TM, Brooke L, Ramsay M, Li TK (2001) Alcohol dehydrogenase-2*2 allele is associated with decreased prevalence of fetal alcohol syndrome in the mixed-ancestry population of the Western Cape Province, South Africa. *Alcohol Clin Exp Res* 25:1719–1722. <https://doi.org/10.1111/j.1530-0277.2001.tb02180.x>
209. Warren KR, Li TK (2005) Genetic polymorphisms: impact on the risk of fetal alcohol spectrum disorders. *Birth Defects Res A Clin Mol Teratol* 73:195–203
210. Edenberg HJ (2007) The genetics of alcohol metabolism: role of alcohol dehydrogenase and aldehyde dehydrogenase variants. *Alcohol Res Health* 30:5–14
211. Stoler JM, Ryan LM, Holmes LB (2002) Alcohol dehydrogenase 2 genotypes, maternal alcohol use, and infant outcome. *J Pediatr* 141:780–785. <https://doi.org/10.1067/mpd.2002.128112>
212. Das UG, Cronk CE, Martier SS, Simpson PM, McCarver DG (2004) Alcohol dehydrogenase 2*3 affects alterations in offspring facial morphology associated with maternal ethanol intake in pregnancy. *Alcohol Clin Exp Res* 28:1598–1606. <https://doi.org/10.1097/01.ALC.0000141816.14776.97>
213. McCarver DG, Thomasson HR, Martier SS, Sokol RJ, Li T-K (1997) Alcohol dehydrogenase-2*3 allele protects against alcohol-related birth defects among African Americans. *J Pharmacol Exp Ther* 283:1095–1101
214. Jacobson SW, Carr LG, Croxford J, Sokol RJ, Li T-K, Jacobson JL (2006) Protective effects of the alcohol dehydrogenase-ADH1B allele in children exposed to alcohol during pregnancy. *J Pediatr* 148:30–37
215. Boyles AL, DeRoo LA, Lie RT, Taylor JA, Jugessur A, Murray JC, Wilcox AJ (2010) Maternal alcohol consumption, alcohol metabolism genes, and the risk of oral clefts: a population-based case-control study in Norway, 1996–2001. *Am J Epidemiol* 172:924–931
216. Ritchie SJ, Bates TC, Corley J, McNeill G, Davies G, Liewald DC, Starr JM, Deary IJ (2014) Alcohol consumption and lifetime change in cognitive ability: a gene x environment interaction study. *Age* 36:1493–1502. <https://doi.org/10.1007/s11357-014-9638-z>
217. Birley AJ, James MR, Dickson PA, Montgomery GW, Heath AC, Martin NG, Whitfield JB (2009) ADH single nucleotide polymorphism associations with alcohol metabolism in vivo. *Hum Mol Genet* 18:1533–1542. <https://doi.org/10.1093/hmg/ddp060>
218. Sherva R, Rice JP, Neuman RJ, Rochberg N, Saccone NL, Bierut LJ (2009) Associations and interactions between SNPs in the alcohol metabolizing genes and alcoholism phenotypes in European Americans. *Alcohol Clin Exp Res* 33:848–857. <https://doi.org/10.1111/j.1530-0277.2009.00904.x>
219. Xu K, Kranzler HR, Sherva R et al (2015) Genomewide association study for maximum number of alcoholic drinks in European Americans and African Americans. *Alcohol Clin Exp Res* 39:1137–1147. <https://doi.org/10.1111/acer.12751>
220. Way M, McQuillin A, Saini J et al (2015) Genetic variants in or near ADH1B and ADH1C affect susceptibility to alcohol dependence in a British and Irish population. *Addiction Biol* 20:594–604. <https://doi.org/10.1111/adb.12141>
221. Taylor M, Simpkin AJ, Haycock PC, Dudbridge F, Zuccolo L (2016) Exploration of a polygenic risk score for alcohol consumption: a longitudinal analysis from the ALSPAC Cohort. *PLoS One* 11:e0167360. <https://doi.org/10.1371/journal.pone.0167360>
222. Zuccolo L, Fitz-Simon N, Gray R, Ring SM, Sayal K, Smith GD, Lewis SJ (2009) A non-synonymous variant in ADH1B is strongly associated with prenatal alcohol use in a European sample of pregnant women. *Hum Mol Genet* 18:4457–4466. <https://doi.org/10.1093/hmg/ddp388>
223. Abel EL (1995) An update on incidence of FAS: FAS is not an equal opportunity birth defect. *Neurotoxicol Teratol* 17:437–443. [https://doi.org/10.1016/0892-0362\(95\)00005-C](https://doi.org/10.1016/0892-0362(95)00005-C)
224. Wilson SE, Cudd TA (2011) Focus on: the use of animal models for the study of fetal alcohol spectrum disorders. *Alcohol Res Health* 34:92–98
225. Cudd TA (2005) Animal model systems for the study of alcohol teratology. *Exp Biol Med* 230:389–393
226. Mukherjee RAS (2015) Letter to editor: reply to Miller. *Child Care Health Dev* 41:636. <https://doi.org/10.1111/cch.12260>
227. Lewis SJ, Relton C, Zammit S, Smith GD (2013) Approaches for strengthening causal inference regarding prenatal risk factors for childhood behavioural and psychiatric disorders. *J Child Psychol Psychiatry* 54:1095–1108
228. Krieger N, Smith DG (2016) The tale wagged by the DAG: broadening the scope of causal inference and explanation for epidemiology. *Int J Epidemiol* 45:1787–1808. <https://doi.org/10.1093/ije/dyw114>
229. Daniel RM, De Stavola BL, Vansteelandt S (2016) Commentary: the formal approach to quantitative causal inference in epidemiology: misguided or misrepresented? *Int J Epidemiol* 45:1817–1829. <https://doi.org/10.1093/ije/dyw227>
230. Hernán MA (2004) A definition of causal effect for epidemiological research. *J Epidemiol Commun Health* 58:265–271
231. Greenland S, Pearl J, Robins JM (1999) Causal diagrams for epidemiologic research. *Epidemiology* 10:37–48
232. Weinberg CR (2007) Can DAGs clarify effect modification? *Epidemiology* 18:569–572. <https://doi.org/10.1097/EDE.0b013e318126c11d>
233. Thompson WD (1991) Effect modification and the limits of biological inference from epidemiologic data. *J Clin Epidemiol* 44:221–232
234. Van der Weele TJ, Robins JM (2007) Four types of effect modification: a classification based on directed acyclic graphs. *Epidemiology* 18:561–568
235. VanderWeele TJ, Robins JM (2007) Directed acyclic graphs, sufficient causes, and the properties of conditioning on a common effect. *Am J Epidemiol* 166:1096–1104
236. Elwert F (2013) Graphical causal models. In: Morgan SL (ed) *Handbook of causal analysis for social research*. Springer, Netherlands, pp 245–273. <https://doi.org/10.1007/978-1094-1007-6094-1003>